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CONTENTS OF PREVIOUS NUMBER

JULY 1943. NUMBER 1

Guide to Replacement Therapy for Loss of Blood or Plasma. Hilger Perry Jenkins, M.D.; Paul W. Schafer, M.D., and Frederick M. Owens, Jr., M.D., Chicago.

Ligation of the Saphenous Vein for Varicose Veins. Captain R. W. Postlethwait, Medical Corps, Army of the United States.

Sarcoma of the Stomach: A Clinical and Pathologic Study. Captain George F. Schroeder, Medical Corps, Army of the United States, and Herbert J. Schattenberg, M.D., San Antonio, Texas.

Treatment of Acute Cholecystitis: A Suggested Two Stage Treatment. Dean Macdonald, M.D., St. Catharines, Ontario, Canada.

Influence of Hepatic Function on Metabolism of Vitamin A. Karl A. Meyer, M.D.; Frederick Steigmann, M.D.; Hans Popper, M.D., and William H. Walters, M.D., Chicago.

Plasma Clot Suture of Nerves: Experimental Technic. I. M. Tarlov, M.D.; C. Denslow, S. Swarz, and D. Pineles, M.D., Brooklyn.

Mechanism of Erythremia: Erythremia Resulting from Traumatic Shock in Dogs and from Injections of Epinephrine into Human Beings and Dogs. R. D. Taylor, M.D., and Irvine H. Page, M.D., Indianapolis.

Angiofibroma of the Ileum: Clinical Picture in Tumors of the Small Intestine. Manuel E. Lichtenstein, M.D., and Frank R. Dutra, M.D., Chicago.

Chronic Effects Resulting from Downward Traction on the Liver. Walter M. Booker, Ph.D., Prairie View, Texas.

Review of Urologic Surgery. Albert J. Scholl, M.D., Los Angeles; Frank Hinman, M.D., San Francisco; Alexander von Lichtenberg, M.D., Mexico, Mexico; Alexander B. Hepler, M.D., Seattle; Robert Gutierrez, M.D., New York; Gershom J. Thompson, M.D., and Edward N. Cook, M.D., Rochester, Minn.; Egon Wildbolz, M.D., Berne, Switzerland, and Vincent J. O'Conor, M.D., Chicago.

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PATHOLOGIC STUDY OF DEGENERATION AND RUPTURE OF THE SUPRASPINATUS TENDON

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Rupture of the tendons of the short rotator cuff of the shoulder joint, notably the supraspinatus tendon, is important because of the frequency of its occurrence and because of the disability that may follow. The whole subject of rupture of the short rotator tendons of the shoulder has been reviewed at length by one of us (C. L. Wilson) in another publication.[1] The purpose of this paper is to present a gross and microscopic study of the supraspinatus tendon at various ages made especially with a view to amplifying the present rather scanty information regarding the pathologic changes in the tendon leading to rupture.

McMaster,[2] from experiments on rabbits, has shown that when a system composed of a muscle and its tendon, together with their bony attachments, is stretched to the breaking point by a force exerted through the bones the break occurs anywhere but in the tendon, unless the tendon has been previously injured. It will be shown in this paper that when a similar system composed of the normal supraspinatus tendon and its attachments is subjected to breaking strain, the break in this system, too, occurs at any point except in the tendon. Therefore, some lesion of the supraspinatus tendon that weakens it must be postulated to account for the occurrence of rupture as observed clinically. Such a lesion has not, hitherto, been specifically described or specifically related to rupture. Indeed, the microscopic observations on degenerative disease and rupture of the supraspinatus tendon have been relatively few and inconclusive. Codman [3] described abnormalities consisting of irregularity in the staining of the fibrocartilage at the tendon insertion, loss of the smooth contour of the thin line of calcified fibrocartilage (the "blue line") at its junction with the bony cortex, changes in the thickness of the latter and what he called hyaline degeneration of the tendon bundles. Lindblom [4] spoke of the latter change in the substance of the tendon as "homogeneous sclerosization." Both these authors expressed the belief that areas of degeneration in the tendon stained more deeply with eosin than their surroundings, a view that is quite the reverse of the

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1. Wilson, C. L.: Lesions of the Supraspinatus Tendon: Degeneration, Rupture and Calcification, Arch. Surg. **46**:307 (March) 1943.

2. McMaster, P. E.: Tendon and Muscle Ruptures: Clinical and Experimental Studies on the Causes and Location of Subcutaneous Ruptures, J. Bone & Joint Surg. **15**:705, 1933.

3. Codman, E. A.: The Shoulder: Rupture of the Supraspinatus Tendon and Other Lesions in or About the Subacromial Bursa, Boston, The Author, 1934.

4. Lindblom, K.: On Pathogenesis of Ruptures of the Tendon Aponeurosis of the Shoulder-Joint, Acta radiol. **20**:563, 1939; Arthrography and Roentgenography in Ruptures of Tendons of the Shoulder, ibid. **20**:548, 1939.

conclusion reached in the present study. However, we are able to confirm that degenerative changes are frequently to be found in the supraspinatus tendon after the age of 30 years. In the body of this paper, a degenerative lesion of the supraspinatus tendon is described in its various stages of development. This lesion is of such a character as to cause weakening of the tendon, and its occurrence shows a close correlation with the occurrence of rupture of the supraspinatus tendon. The findings are such as to justify the conclusion that the lesion described is responsible for the weakening of the tendon that leads finally to rupture.

MATERIALS AND METHODS

Both shoulders were examined in an unselected series of 90 bodies at autopsy and 35 anatomic cadavers, the total number of bodies examined thus being 125. The method of gross examination was to extend the routine autopsy incision up to the tip of the shoulder and then to free the skin from the underlying tissues. The deltoid muscle was divided transversely, with the arm in the anatomic position to insure exposure of the subacromial bursa, which was then opened. To give adequate exposure of the short rotator cuff, the coracoacromial ligament was divided. The next step was to locate and examine the tendon of the long head of the biceps muscle in the bicipital groove. If the tendon was found to be intact, a knife was passed up the groove, medial to the tendon, cutting the transhumeral ligament, the joint capsule and the few overlying blending fibers of the supraspinatus and subscapularis tendons. This incision was carried up past the musculotendinous junction of the supraspinatus muscle, across the muscle and down the other side of the tendon to its insertion on the greater tuberosity. In the autopsy series the tendon and its bony attachment were removed intact and inspected for rupture. A rupture of one or more of the tendons of the short rotator cuff was recorded as a complete rupture when it allowed free communication between the subacromial bursa and the cavity of the shoulder joint. A partial tear of the fibers that did not allow free communication between the subacromial bursa and the shoulder joint was counted as a partial rupture. The length of the intact tendon was measured, and then the specimen was preserved in Helly's or Zenker's solution for histologic examination. In the autopsy series the circumference of each arm at the level of the belly of the biceps was noted and the spinal column was inspected for scoliosis and vertebral lipping.

The specimens for histologic examination, including bone, were decalcified in an aqueous solution made up of equal parts of 50 per cent formic acid and 20 per cent sodium citrate. The histologic sections were stained routinely with hematoxylin and eosin and with Mallory's stain for connective tissue. Selected sections were stained with Weigert's and Verhoeff's stains for elastic tissue, stains for mucin, Van Gieson's stain for connective tissue and Perles' stain for iron. Since the bone contained in all of these sections had been decalcified, a control set of sections was made of tendons that had not been exposed to the action of the decalcifying solution, to determine whether decalcification had any effect on the staining properties of the tendons. When it had been established that the staining properties were unaffected by decalcification, controls were discontinued.

The tensile strength of various tendons other than the supraspinatus was determined by use of tendon clamps which were modified from Cronkite's clamp.[5] The tensile strength of a limited number of supraspinatus tendons and muscles and their bony attachments was measured by pulling the system apart by a force applied through steel pins inserted in the bones. In these experiments a Tinius Olsen Universal Tension Machine, accurate to 0.5 per cent, was used.

OBSERVATIONS

Incidence of Rupture.—Since rupture of the supraspinatus tendon has never been reported in a patient less than 32 years of age,[1] only subjects over 30 years of age were used in assessing the frequency of rupture. This excluded 16 bodies from the autopsy series and 1 from the cadaver group. In the autopsy series complete rupture occurred in 15 of 74 bodies over 30 years of age, that is, an incidence of 20 per cent. There were 8 unilateral ruptures and 7 bilateral.

In the cadaver group complete rupture occurred in 9 of 34 bodies, an incidence of 26.5 per cent. Four ruptures were unilateral, and 5 were bilateral.

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[5] Cronkite, A. E.: Tensile Strength of Human Tendons, Anat. Rec. **64**:173, 1936.

The average age of all autopsy subjects over 30 was 55 years and of cadaver subjects 66 years. In spite of this, the average age of subjects with complete rupture was virtually the same in the two groups. In both groups taken together, the average age of the subjects with complete rupture was 65 years and the incidence was 22.2 per cent of the bodies examined. The youngest subject with complete rupture was a man 48 years of age, and the oldest was a woman 87 years of age. The incidence among men was 23.7 per cent and among women was 17.8 per cent.

In the autopsy series unilateral complete rupture occurred on the right side six times and on the left side twice. In every instance of unilateral complete rupture the circumference of the arm at the level of the belly of the biceps was at least 1 cm. greater on the side of the rupture than on the opposite side. In the cadaver series, in which no measurements of arm circumference were made, the unilateral complete ruptures all occurred on the right side. It should also be noted that in both series whenever a bilateral rupture occurred the defect in the rotator cuff was always larger on the right side.

Partial rupture of the supraspinatus tendon observed in the autopsy series occurred in 15 subjects of 74 over 30 years of age, an incidence of 20 per cent. Eight of the ruptures were unilateral, three were bilateral and four were unilateral but were associated with a complete rupture of the supraspinatus tendon of the opposite side. Of the eight unilateral partial ruptures, six occurred on the right side and two on the left side. In all but 1 of the bodies the rupture was on the side of which the arm had the greater circumference when measured around the belly of the biceps. Not much difference was noted in the size of the partial ruptures between the two sides when the rupture was bilateral. Of the four partial ruptures associated with a complete rupture of the opposite supraspinatus tendon, two occurred on the right and two on the left. The partial ruptures were all on the side of the smaller arm, and the complete ruptures were on the side of the larger arm. The average age incidence of partial rupture of the supraspinatus tendon was 62 years.

In 8 persons out of the 108 over 30 years of age, there was rupture of the long head of the biceps tendon as well as complete or partial rupture of the supraspinatus tendon, an incidence of 7.4 per cent. Four of the subjects had bilateral rupture and four unilateral (12 ruptures in all).

Gross Observations.—As one would expect, the supraspinatus tendon is longer in an adult than in a child. Measurements of the tendon in subjects of different ages showed, however, that once adult age was reached the normal tendon did not increase in length with increasing age. It should be emphasized that since the muscle inserts into the tendon in semicircular fashion it is necessary to measure the tendon after it has been split through the middle in order to obtain consistent measurements. It is also important to note that abnormality of the tendon short of complete rupture can cause measurable lengthening. In 23 adult subjects of different ages, the supraspinatus tendons on superficial examination appeared normal but the measurements showed that the right tendons averaged 0.4 cm. longer than the left. It was then discovered on more careful examination that a number of the tendons from the right side were not really normal. These showed a partial rupture involving the joint capsule and adjacent fibers of the tendon, which had lost their attachment to the sulcus and the greater tuberosity of the humerus. This type of lesion, known as a rim rent, causes a decrease in the thickness of the tendon at its insertion and a definite increase in its total length. When this source of error was corrected by omitting persons with rim rent, it was found in a series of 40 subjects with normal supraspinatus tendons that the

tendons were of equal length on the two sides, averaging 2.25 cm. on each side. Only 2 of these subjects were left handed, as judged by a larger circumference of the left arm measured at the level of the belly of the biceps muscle.

The gross pathologic changes in rupture of the supraspinatus tendon have been described adequately in the literature.[6] The observations in the present study, confirming those of previous investigators, were briefly as follows: Partial ruptures were characterized by the presence of a tear near the insertion of the tendon but involving only a part of its thickness and not forming an open rent that would allow communication between the joint cavity and the subacromial bursa. Such incomplete ruptures in some instances involved the fibers nearest the joint cavity (rim rent) and in others the tendon layer just beneath the subacromial bursa; in still others they involved the central part of the thickness of the tendon without affecting either surface. In the complete ruptures there was a tear across the

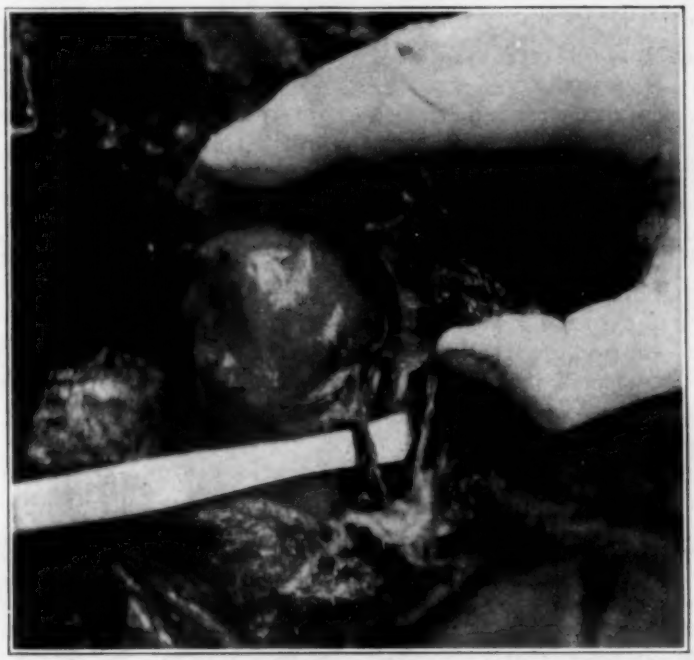

Fig. 1.—Photograph of dissection of the right shoulder joint. The tendons of insertion of the supraspinatus, infraspinatus and teres minor muscles and the capsule of the shoulder joint have torn away, the head of the humerus thus being allowed to come into direct contact with the under surface of the deltoid muscle. There are extensive erosion of the head of the humerus and recession of the greater tuberosity. The intra-articular portion of the tendon of the long head of the biceps muscle has been lost, while the lower portion (indicated by the scalpel passed beneath it) has become attached at its upper end to the bicipital groove.

6. (*a*) Davis, T. W., and Sullivan, J. E.: Rupture of the Supraspinatus Tendon, Ann. Surg. **106**:1058, 1937. (*b*) Horwitz, M. T.: Lesions of the Supraspinatus Tendon and Associated Structures: Investigation of Comparable Lesions in Hip-Joint, Arch. Surg. **38**: 990 (June) 1939. (*c*) Keyes, E. L.: Observations on Rupture of Supraspinatus Tendon Based on Study of Seventy-Three Cadavers, Ann. Surg. **97**:849, 1933; Cadaver Observations: Anatomical Observations on Senile Changes in the Shoulder, J. Bone & Joint Surg. **17**:953, 1935. (*d*) Meyer, A. W.: Further Evidences of Attrition in the Human Body, Am. J. Anat. **34**: 241, 1925-1926; Unrecognized Occupational Destruction of the Tendon of the Long Head

(Footnote continued on next page)

supraspinatus tendon near its insertion, sometimes extending to involve the tendons of the infraspinatus, teres minor or subscapularis muscles. The defects thus produced allowed free communication between the cavity of the shoulder joint and the subacromial bursa. Complete ruptures of some duration showed retraction, thickening and rounding of the torn edges with the formation of a triangular defect, the base of which was on the greater tuberosity of the humerus. If the rupture was recent the latter bore the stub of the ruptured tendon, but if the rupture was of longer standing the torn end of the tendon attached to the greater tuberosity was scarcely discernible, or had disappeared altogether (fig. 1).

In cases of rim rent or of complete rupture of the supraspinatus tendon, associated changes of varying degree in the articular cartilage of the head of the

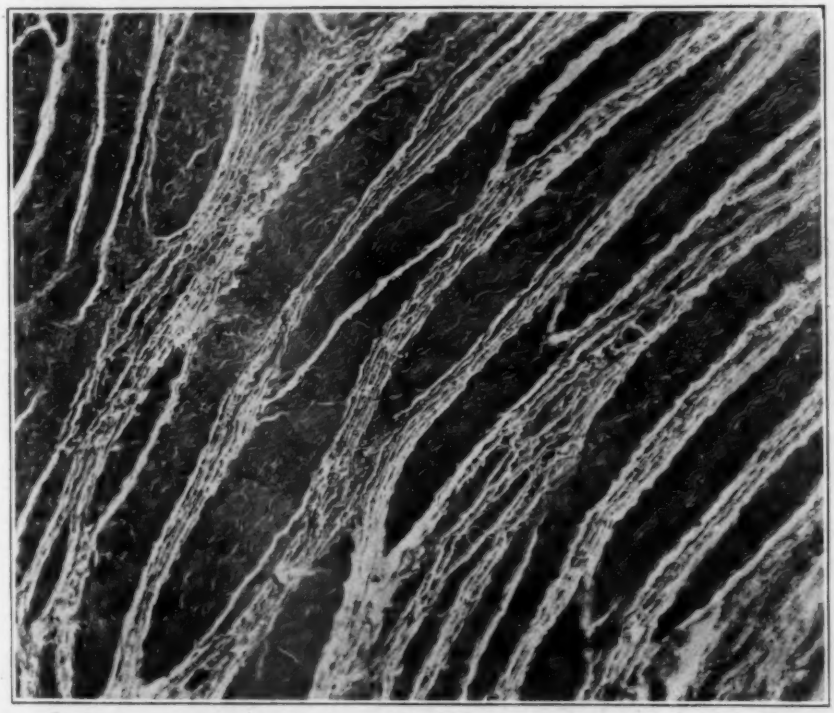

Fig. 2.—Photomicrograph of a histologic section of normal supraspinatus tendon, showing the typical arrangement of the wavy collagen bundles and the thin elongated nuclei of fibrous connective tissue cells. Note the absence of visible blood vessels. Hematoxylin and eosin; × 98.

humerus were frequently seen. These consisted of slight roughening, fraying or erosion of the cartilage in a position corresponding with that of the defect in the supraspinatus tendon but involving an area somewhat larger than that of the defect in the tendon. Moreover, there appeared to be a relation between the

of the Biceps Brachii, Arch. Surg. **2**:130 (Jan.) 1921; Chronic Functional Lesions of the Shoulder, ibid. **35**:646 (Oct.) 1937. (*e*) Skinner, H. A.: Anatomical Considerations Relative to Rupture of the Supraspinatus Tendon, J. Bone & Joint Surg. **19**:137, 1937. (*f*) Wilson, P. D.: Complete Rupture of the Supraspinatus Tendon, J. A. M. A. **96**:433 (Feb. 7) 1931; The Painful Shoulder, Brit. M. J. **2**:1261, 1939. (*g*) Codman.[3]

occurrence of pronounced changes in the articular cartilage and rupture of the tendon of the long head of the biceps muscle. In all cases of rupture of the biceps tendon there was definite erosion of the cartilage of the head of the humerus, over which the intracapsular portion of the biceps tendon had run. In 10 instances there was a complete rent in the supraspinatus tendon through which the roughened and eroded head of the humerus could be seen when the subacromial bursa was opened. In the other 2 instances there was only a rim rent of the supraspinatus tendon and less erosion of the head of the humerus. In 10 of the instances of rupture of the biceps tendon, the upper end of the lower portion of the tendon was fused to the bicipital groove (fig. 1), and in 2 of these there was also an attachment to the transhumeral ligament, the biceps tendon being apparently split

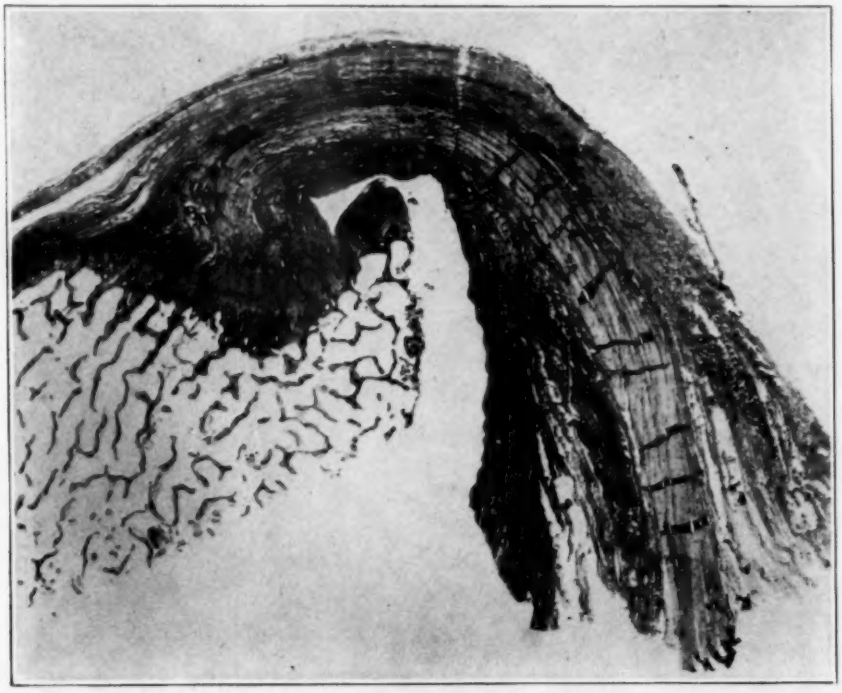

Fig. 3.—Photomicrograph of a histologic section of normal supraspinatus tendon and its insertion. The dark borders on the upper and lower surfaces of the tendon aponeurosis represent the base of the subacromial bursa and the capsule of the shoulder joint, respectively. Only the pale central portion is true tendon. Mallory's stain for connective tissue; × 4.2.

in two. In these 10 instances of rupture, there was no discernible remnant of the biceps tendon above the transhumeral ligament. In 2 instances the biceps tendon showed no attachment to the bicipital groove but the intracapsular portion was fused to the under surface of the joint capsule, leaving no free portion within the joint. The glenoid attachment of the tendon was discernible as a bandlike structure.

Microscopic Observations.—Microscopic study of the supraspinatus tendon in subjects of different ages showed that the tendon bundles increase in diameter and presumably in length from infancy to adult life. In all normal tendons the

wavy appearance of discrete collagen bundles was readily seen but the fibroblasts lying between the bundles were represented only by elongated dark nuclei lying parallel with the collagen fibers (fig. 2). It should be noted that the tendon forms only part of the depth of the tissue composing the musculotendinous cuff. The rest is made up of the base of the normally thin subacromial bursa above and the capsule of the shoulder joint below. Codman's sketch [3] does not show this point, but it is brought out clearly with Mallory's stain for connective tissue, which colors the base of the bursa and the joint capsule blue and the tendon orange (fig. 3). The number of arterioles has been found by many to decrease with

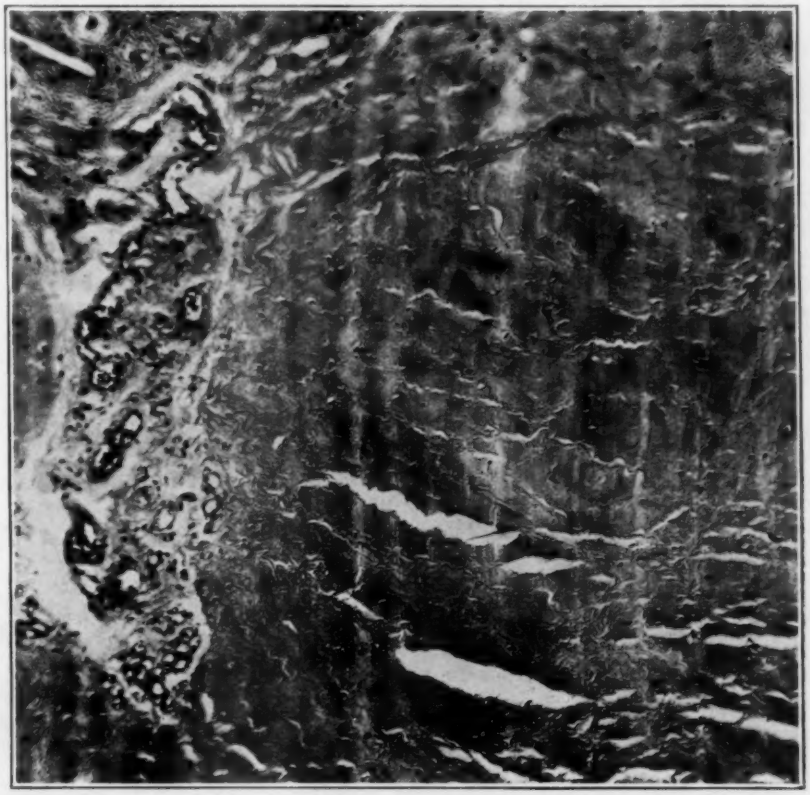

Fig. 4.—Photomicrograph of a histologic section of supraspinatus tendon near its insertion, showing loss of normal wavy outline of tendon bundles, with fusion into a homogeneous mass, in which the nuclei of connective tissue cells are distorted, rounded or pyknotic. There is a downgrowth from the floor of the subacromial bursa of loose fibrous tissue containing many thick-walled blood vessels. Hematoxylin and eosin; × 110.

age.[7] This was confirmed in the present study. Numerous arterioles were seen in the supraspinatus tendon in infancy and childhood, but the number gradually decreased up to 40 years of age. After the age of 40 years, arterioles were seen relatively rarely in normal tendons.

7. Rau, cited by Honigsman, F.: Med. Klin. **22**:728, 1926. Sobotta, J.: Atlas of Human Histology and Microscopic Anatomy, translated by W. H. Piersol, New York, G. E. Stechert & Company, 1930. McMaster.[2]

Special stains were used to study the component parts of the suprapinatus tendon. No elastic tissue could be demonstrated in the tendons or at most only a few very fine fibrils. Stains for mucin and for iron produced negative results in both normal and degenerate tendons. Decalcification in formic acid–sodium citrate solution did not affect the staining reactions of tendons to hematoxylin and eosin or to Mallory's stain for connective tissue. A normal tendon stains a deep pink with eosin and orange with Mallory's stain. The structure of the supraspinatus tendon just before it inserts into the bone is that of fibrocartilage, and where it joins the bony cortex a narrow band becomes calcified and forms a blue line when stained with hematoxylin.

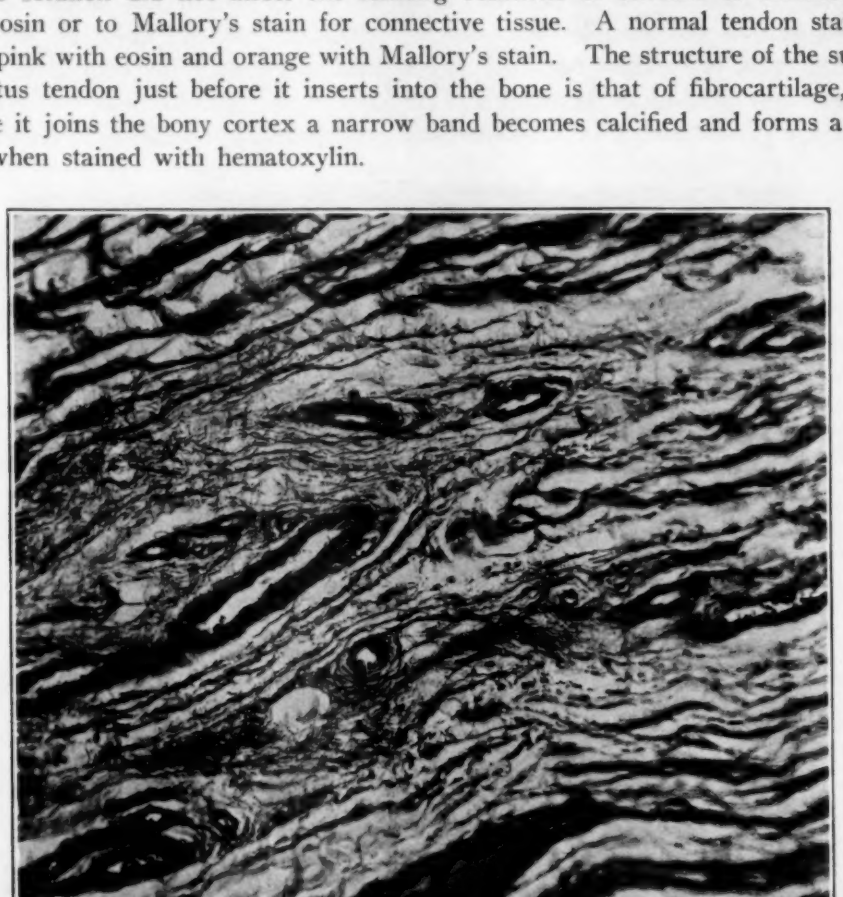

Fig. 5.—Photomicrograph of a histologic section of supraspinatus tendon near its insertion, showing a more advanced stage of degeneration. The fibrillar tendon structure has a loose edematous appearance. Note the numerous thick-walled arterioles. Hematoxylin and eosin; × 104.

In many of the subjects with intact supraspinatus tendons, certain degenerative changes in these tendons were observed on microscopic examination. These changes tended to be greater in degree with advancing years. They were more prominent than would be expected on the basis of age alone in those who, to judge by their clinical history, had done heavy manual labor. Changes of the same kind were found in still more pronounced degree in partially ruptured supraspinatus tendons, and the most severe alterations were seen in tendons which had ruptured completely. It seemed evident that the observed abnormalities bore some relation to the spontaneous occurrence of partial or complete rupture of the supraspinatus tendon.

The degenerative changes referred to in the supraspinatus tendon were characterized by alterations in the tendon itself and also in its insertion. The earliest histologic evidence of abnormality in the structure of the tendon in sections stained with hematoxylin and eosin was a granularity and loss of the normal clear wavy outline of individual collagen fibers and bundles of such fibers. They became straighter and tended to merge with one another so that individual fibers and bundles were obscured and the whole structure took on a rather homogeneous appearance (fig. 4). Such homogeneous strands in the tendon stained less deeply with eosin than the normal portions. The arrangement of the nuclei of connective tissue cells became somewhat disordered; they lay with their long axes in various directions, not necessarily parallel with the direction of the collagen fibers. Moreover, the nuclei had a shrunken, distorted appearance; some of them were rounded, vesicular and rather faintly stained with hematoxylin while others were pyknotic (fig. 4). With the further development of these changes, the homogeneous areas in the tendon took on a somewhat gelatinous or edematous appearance, with a loosening of the constituent fibers, which again became visible. However, these fibers no longer had the plump, smooth appearance of normal collagen but consisted of a sparse and broken network of frayed and shredded threads widely separated by a pale-staining homogeneous material that suggested a fluid or semifluid consistency (fig. 5). The homogeneous interfibrillar material did not give the staining reactions of mucin. The fibrillar appearance of the tendon structure at this stage must be differentiated from a somewhat similar appearance that may be produced as an artefact in cutting sections from blocks of tissue in which the bone has been insufficiently decalcified.

In histologic sections stained with Mallory's stain for connective tissue, progressive changes in staining properties ran parallel with the alterations just described. The collagen bundles of the normal tendon stain a brilliant orange with this stain, the color being uniformly and smoothly spread along the fibers. In degenerating tendons, however, the orange staining first became irregular. Small patches in the bundles of collagen fibers showed no orange staining or were only lightly stained, while in neighboring areas there appeared little accumulations or "pools" of a homogeneous material resembling a thick fluid which stained deeply orange. The loss of the staining properties of tendon bundles progressed in patchy fashion until only a few small areas showed any staining with orange and the remainder stained blue instead. The little "pools" of orange-staining material did not become large but remained visible in degenerated areas bordering on those parts of the tendon in which more or less normal staining still prevailed. This progressive loss of the orange-staining property corresponded with alterations in the tendon leading to the homogeneous appearance already described as seen in sections stained with hematoxylin and eosin. In tendons that had passed beyond the "homogeneous" stage and showed fibrillation, the greater part of the tendon stained blue with Mallory's stain and only small scattered areas were tinged with orange. The whole degenerative process as observed in sections stained with Mallory's stain suggested that the normal orange-staining property of the tendon depended on impregnation of the fibers by some viscid substance which was progressively lost as the process became more advanced. This suggestion is supported by the fact that normal tendons treated by immersion in a normal solution of sodium hydroxide for one to twelve hours at room temperature stained uniformly blue with Mallory's stain and showed a complete loss of the normal orange staining, as though the substance responsible for this characteristic staining property had been dissolved out of the tendon.

As the degenerative changes just described became more advanced, there was an evident increase in the number of blood vessels in the degenerating areas. Small arterioles apparently connected with those of the subacromial bursa and the joint capsule invaded the degenerating areas accompanied by a small amount of loose connective tissue (figs. 4 and 5). Such an invasion of blood vessels into the substance of the tendon was never observed in persons over 40 years of age except in association with degenerative changes in the tendon of the character already described.

Alterations in the supraspinatus tendon were not infrequently accompanied by changes at its insertion. The fibrocartilage was in some instances rendered homogeneous and in others fibrillar, in either case staining very lightly with eosin. Abnormalities in the bony cortex of the greater tuberosity consisted of thinning or thickening or irregularity of this layer (fig. 6) with or without actual perforation of the cortex by loose connective tissue containing many thick-walled blood vessels and giant cells.

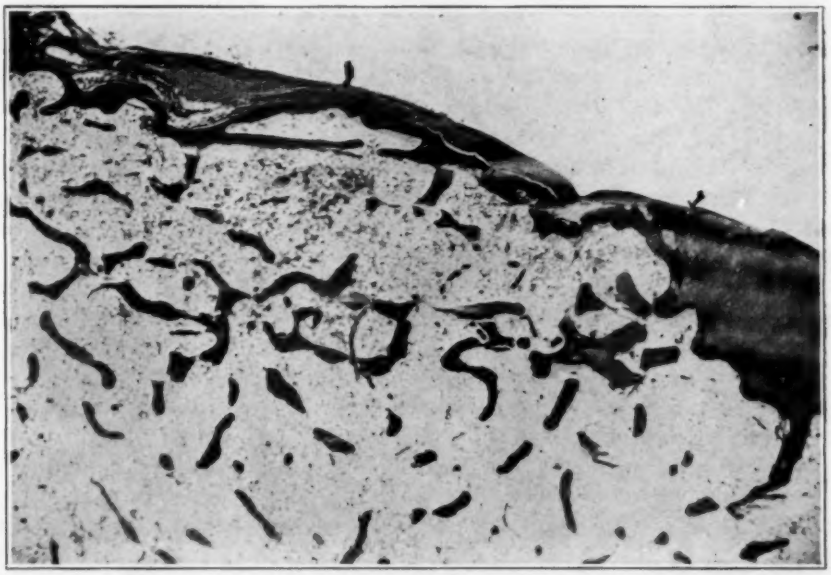

Fig. 6.—Photomicrograph of a histologic section of the greater tuberosity of the humerus, showing recession following complete rupture of the supraspinatus tendon. At the site of insertion of the tendon there is no remnant of tendon or fibrocartilage but only a thin layer of loose connective tissue covering the abnormally thin bony cortex. The margin of the articular cartilage is seen at the right side of the photograph. Hematoxylin and eosin; × 21.

An attempt was made to grade the degree of degeneration on a four point scale by scoring one point for each of the following features: (1) alterations in the structure of the tendon; (2) distinct changes in staining qualities; (3) increase in the number of arterioles, and (4) abnormalities at the tendon insertion. A grade of 0 represented a normal tendon, while a grade of IV represented the maximum degree of degeneration. The latter was encountered almost exclusively in ruptured tendons. Eighty-four supraspinatus tendons from the right side and 85 from the left side were graded on this basis, and the results are set out in the table, which serves to show clearly the relation of age to the degree of severity of degenerative changes in the supraspinatus tendon.

In a limited number of cases the tendon of the long head of the biceps muscle was examined microscopically. Its normal structure was found to be the same as that of the supraspinatus tendon. Degenerative changes were also observed. These were of the same kind and were characterized by the same features as already described in the supraspinatus tendon. The degree of degenerative change in the tendon of the long head of the biceps was generally comparable to that of the supraspinatus tendon of the same shoulder.

Tensile Strength.—By tests on tendons taken from various locations in the body, it was found that a tendon about 0.5 cm. in diameter would withstand a tension of over 200 pounds (90 Kg.) when the ends of the tendons, secured in special clamps, were gradually and evenly pulled apart in the tension machine. In tests of the strength of the system composed of the head of the humerus, the supraspinatus tendon and muscle and the scapula, the tension was applied slowly through pins inserted in the bones. It was found that a break generally occurred at a tension of a little less than 175 pounds (80 Kg.) and that the break occurred anywhere but in the tendon. Microscopic examination of the tendons from the specimens that had been broken in this way revealed normal or only slightly abnormal structure.

Age Distribution of Degenerative Changes in Supraspinatus Tendon

	Grade of Degeneration				
	0	I	II	III	IV
Right Supraspinatus Tendon:					
Average age of patients in each grade in years....	32.4	47.5	60.3	60.2	69.4
Number of tendons in each grade.....	27	16	14	18	9
Percentage of tendons in each grade.....	32.1	19.1	16.7	21.4	10.7
Left Supraspinatus Tendon:					
Average age of patients in each grade in years....	33.3	51.1	58.9	58.3	71.9
Number of tendons in each grade.....	28	21	17	11	8
Percentage of tendons in each grade.....	33	24.7	20	12.9	8

COMMENT

Skinner [6e] has stated that the increased length of the tendon which occurs with age is at the expense of the muscle at the musculotendinous junction. As has been shown in the present study, a rim rent gives an apparent increase in the length of the supraspinatus tendon, but obviously a rim rent can be disregarded as one of the factors causing normal increase in the length of the tendon. In the tendons of children and adolescents there were no signs of replacement of muscle by tendon at the musculotendinous junction. That is to say, there were no intermediate stages to support Skinner's theory of muscle replacement. The fact that the average length of the supraspinatus tendons on the right and on the left side was the same would throw further doubt on Skinner's idea, since, according to his theory, use of the arm causes muscle to be replaced by tendinous tissue; if this were true, the tendon on the right in a right-handed person would be longer than the one on the left, which it is not except when a rim rent is present. It is therefore entirely reasonable to assume that the increase in width and presumably also in length of the collagen bundles of the tendon which occurs between infancy and adult age, and which can be easily seen microscopically, is enough to account for the length of an adult supraspinatus tendon.

The figures recorded in the literature on the incidence of complete rupture of the supraspinatus tendon are rather misleading, because they have usually been

based on the number of shoulders examined. A much more accurate concept is obtained if the incidence is based on the number of bodies examined, because then a case is still only 1 case whether rupture is unilateral or bilateral. The lesion is common in the older age groups, and the older the group the more frequently the lesion occurs. This is borne out in the present study by comparison of the incidence, of 20 per cent, in the autopsy series, in which the average age of the group was 55 years, and the considerably higher incidence, of 26.5 per cent, in the series of anatomic cadavers, in which the average age of the group was 11 years greater. It is worthy of note, however, that regardless of the different average ages of the two groups from which the material was drawn, the average ages of the subjects with rupture in the two groups were virtually the same, namely 65 years. This age incidence is in accord with that reported by previous investigators.[1]

In the autopsy material, the circumference of the arm at the level of the belly of the biceps was taken as an indication of handedness, or at least as an indication of the relative degrees of muscular work which had been demanded of the arms during life. The arm with the larger circumference, excluding edema, was considered to be the arm that had been put to greater muscular use. This was checked by the direction of scoliosis if present, with complete agreement in all instances. In the 8 cases of unilateral complete rupture (6 ruptures on the right side and 2 on the left), the results were always consistent with the idea that a unilateral complete rupture occurs on the side that has been called on for greater muscular effort. In all cases of bilateral complete rupture the right arm was larger and more muscular than the left, as judged by the measurements of circumference, and in all the size of the rupture was much larger on the right side than on the left. The 8 unilateral partial ruptures, with 1 exception, occurred on the side of the larger arm. In the 4 cases of partial rupture associated with complete rupture of the opposite side, the partial rupture was always on the side of the smaller arm and the complete rupture on the side of the larger arm. These observations point inevitably to the conclusion that physical use of the arm is an important factor in the causation of rupture of the supraspinatus tendon, with or without associated rupture of the other rotator tendons of the shoulder joint.

It would seem that rupture of the supraspinatus tendon, either complete or partial, in the form of a rim rent, and subsequent erosion of the articular cartilage of the head of the humerus were in some way responsible for a large percentage of the ruptures of the tendon of the long head of the biceps. From the various pictures described of rupture of the long head of the biceps tendon, it is probable that the sequence of events is as follows: First there is degeneration of the supraspinatus tendon, followed by rupture, either complete or partial. Then the articular cartilage of the head of the humerus is eroded by friction against the under surface of the acromion or the coracoacromial ligament in case of complete rupture of the supraspinatus tendon or against the roughened fibers of the supraspinatus tendon in case of a rim rent. The tendon of the long head of the biceps becomes swollen and later frayed as it passes over the roughened head of the humerus. At this stage it shows microscopically the same degenerative changes as those described in the degenerate supraspinatus tendon. The long head of the biceps tendon then becomes attached to the joint capsule, with which in time it is indistinguishably blended throughout its entire intracapsular course. At the same time the roughened biceps tendon becomes attached to the humerus at the top of the bicipital groove. The end result is attachment to the bicipital groove and complete loss of the intracapsular portion.

McMaster's experiments on rabbits [2] and the experiments on tensile strength of the human supraspinatus tendon carried out in the present study show clearly that the normal tendon is, if not the strongest link, at least never the weakest in the bone-muscle-tendon-bone system. The normal human supraspinatus tendon will withstand a tension approaching 175 pounds (80 Kg.) without the occurrence of rupture. Indeed, the break occurs anywhere but in the tendon. In view of these facts, the clinical occurrence of rupture of the supraspinatus tendon makes it perfectly clear that prior changes must have occurred in order to permit rupture of the tendon rather than of some other part of the system. It is obvious, too, that these prior changes must be of such a character as to cause weakening of the tendon. The degenerative changes in the supraspinatus tendon described in this paper answer these requirements fully. These degenerative changes are seen more frequently and in increasing severity with increasing age, reaching a peak in the seventh decade, in which rupture most frequently occurs. They are more pronounced in men than in women and occur especially in persons who have been engaged in heavy manual work. The most advanced degenerative changes are seen in partially or completely ruptured tendons. Apart from this close correlation with the incidence of clinical rupture, the degenerative alterations observed microscopically are of a kind that would lead to weakening of the tensile strength of the tendon. It has already been pointed out that the microscopic appearances, particularly in sections stained with Mallory's stain for connective tissue, suggest a loss of some sort of binding substance from among the tendon fibers. On all of these grounds, it appears reasonable to believe that the microscopic alterations of degenerative character described in this paper constitute the cause of weakening which permits rupture of the supraspinatus tendon when a sudden, perhaps slight strain is applied.

From the data provided by this study, it is evident that age and mechanical use of the shoulder joint are important factors in causing the degeneration of the supraspinatus tendon that leads to rupture. Both the degenerative changes in the tendon and the incidence of rupture increase with advancing years, and both occur with unexpected frequency in persons who can be supposed to have done heavy manual labor. Moreover, degenerative changes are more advanced in the supraspinatus tendon of the shoulder on the more muscular side, and ruptures are more frequent on the more muscular side, both of which observations support the view that use as well as age is important in the causation of degeneration of the tendon.

While these points are clear, it is not so obvious how age and use are effective in bringing about the observed alterations in the supraspinatus tendon leading to rupture. Whether mechanical compression or attrition is able to produce the changes described in the tendon is unknown. The possible role of ischemia in this connection is difficult to evaluate. It appears that the vascularity of the supraspinatus tendon normally decreases with age in a progressive fashion, so that after the age of 40 arterioles are seldom seen in normal tendons. It might be supposed that this decrease of blood supply left the tendon with insufficient nutrition. On the other hand, however, it is found that degenerating tendons possess considerable numbers of arterioles, which are especially numerous in the most degenerated areas, definitely more numerous than normal. This might be regarded either as a "compensatory" ingrowth of new vessels to supply a part possessing insufficient circulation or as an attempt at repair of a pathologic lesion by the ingrowth of vascular connective tissue. The latter view seems much more probable. The influence of age as such is extremely difficult to separate from the influence of use, but age may be accompanied by a deterioration of the fibers composing the tendon through the

occurrence of alteration in the colloidal state of their constituents. Other factors as yet unknown may prove to be even more directly concerned than any of those mentioned, and for the time being one can state only that the pathogenesis of degeneration of the tendon is a problem of which practically nothing is known although the importance of at least two etiologic factors, age and use, seems to be clearly established.

It appears highly probable that the degenerative lesions described in the supraspinatus tendon are not by any means peculiar to that tendon. Similar changes were observed in the tendon of the long head of the biceps muscle. Indeed, it seems reasonable to suppose that changes of the same order and of similar origin may occur in various other tendinous structures in other parts of the body. Some indication that this may be so is furnished by a comparison of data regarding rupture of the supraspinatus tendon with equivalent data given by Donohue[8] concerning rupture of the annulus lamellosus of the intervertebral disk, which permits extrusion of the nucleus pulposus. Both occur in patients over 30 years of age, and the incidence of both increases with the age of the group examined. The incidence of the two lesions is about 15 to 20 per cent of the number of bodies in which it is looked for. Both lesions are more common in men. With both, degeneration of the tendon precedes and is the cause of rupture. With both, the clinical history is that of a minor incidental trauma precipitating the rupture and causing the onset of acute symptoms. The analogy is so striking that it seems probable that these two lesions represent the result of the same process of degeneration of a tendon proceeding in different parts of the body.

SUMMARY AND CONCLUSIONS

Gross and microscopic studies were made of the short rotator tendons of the shoulder joint with special reference to the supraspinatus tendon. These tendons, together with the tendon of the long head of the biceps muscle, were examined in both shoulders in an unselected series of 125 bodies.

The average lengths of the supraspinatus tendons on the right and left sides were the same. Normal growth accounts for the increase in the length of the supraspinatus tendon which is observed from infancy to adult age. A tear of the innermost fibers of the supraspinatus tendon which includes the joint capsule (rim rent) gives an apparent increase in the length of the tendon and occurs most often and is most severe, if bilateral, on the side which has had greater use, that is, the right side.

The frequency of rupture of the supraspinatus tendon increases with the age of the group examined. The incidence of complete rupture among 108 unselected bodies over the age of 30 years was 22.2 per cent. The average age of subjects with complete rupture was 65 years. The incidence of partial rupture among 74 unselected bodies over the age of 30 years was 20 per cent, and the average age of subjects with partial rupture was 62 years.

Complete rupture of the supraspinatus tendon occurs first on the side which has been called on for greater muscular use, and in the case of bilateral rupture it is larger on that side. Therefore the majority of unilateral ruptures are on the right side, and in the case of a bilateral rupture the larger defect is on the right side.

Rupture of the tendon of the long head of the biceps muscle occurred in 7.4 per cent of the bodies examined. It was always associated with complete or partial rupture of the supraspinatus tendon and erosion of the articular cartilage of the head of the humerus. Complete or partial rupture of the supraspinatus

8. Donohue, W. L.: Pathology of the Intervertebral Disc, Am. J. M. Sc. **198**:419, 1939.

tendon is much the most frequent, if not the only, cause of rupture of the tendon of the long head of the biceps other than severance of the tendon by a penetrating wound. After rupture of the supraspinatus tendon, the upper end of the tendon of the long head of the biceps muscle fuses with the capsule of the shoulder joint and is gradually obliterated, while the lower end becomes attached to the bicipital groove.

Weakening of the supraspinatus tendon is a necessary antecedent to rupture. When a strain is applied through the bones to a specimen consisting of scapula, supraspinatus muscle, tendon and humerus, a normal supraspinatus tendon does not rupture. Rupture occurs instead in any other part of the system.

A degenerative lesion of the supraspinatus tendon is described which is characterized by alterations in tendon structure, changes in the staining qualities and increase in the number of arterioles as well as by alterations at the insertion of the tendon. These alterations need not all be present in a given tendon, but they increase with age and may all be present in high degree. They are especially conspicuous in ruptured tendons. It is concluded that this degenerative lesion is the cause of the weakening which permits rupture of the supraspinatus tendon. Similar degenerative changes are found in the tendon of the long head of the biceps muscle.

It is pointed out that the degenerative process described as occurring in the supraspinatus tendon and the tendon of the long head of the biceps muscle probably occurs in varying degrees in other similar structures in other parts of the body. This suggestion is supported by comparison of the known data concerning degeneration and rupture of the supraspinatus tendon with the equivalent data regarding rupture of the tendinous ring of the intervertebral disk.

Prof. C. P. Martin, Department of Anatomy, McGill University, gave us permission to examine the shoulder joints in the series of anatomic cadavers referred to in this paper, and Dean Brown, of the Faculty of Engineering, placed at our disposal the apparatus used for measuring the tensile strength of the tendons.

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ANATOMIC AND CLINICAL STUDY OF THE TRANSVERSE ABDOMINAL INCISION

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The transverse abdominal incision has been used nearly one hundred years. Baudelocque [1] used it prior to 1847 for cesarean sections, but it was Pfannenstiel,[2] in 1900, who popularized its use in pelvic operations. Maylard [3] (1899), of Glasgow, first used a transverse incision in the upper part of the abdomen. In making this incision, he sectioned all layers of the abdominal wall in a transverse plane. An intra-abdominal hemorrhage that occurred after the closure of a median vertical incision led him to employ a transverse incision for the second laparotomy. He subsequently observed that the transverse section healed more quickly and more firmly than the median vertical one, in which a hernia developed.

Boeckmann,[4] of St. Paul, unaware of Maylard's observations, first employed the transverse incision in all types of abdominal operations in 1906. Sprengel [5] introduced it to the Continental surgeons in 1910 and, in conjunction with Bakes, pointed out many of its advantages.[5] Since 1910 advocates of the transverse abdominal incision have been fairly numerous. Moschcowitz [6] (1916), Quain [7] (1917), Moore [8] (1922), Sloan [9] (1927) and Bartlett and Bartlett [10] (1933) have been especially interested in the problem. At the present time the transverse incision is being used by many surgeons; however, its acceptance as the abdominal incision of election is not as widespread as it should be.

As opinions on vertical and transverse incisions vary among authors, and in view of the apparent increase in popularity of the transverse variety, it was felt that an investigation of it would be timely. It was noted early that opinions and descriptions on the anatomy of the abdominal wall varied and that descriptions in standard texts were at variance with more recent work.[11] Careful anatomic dissections of the anterior abdominal wall were then carried out. To evaluate the clinical aspects of the transverse incision a series of 225 consecutive transverse incisions in the upper part of the abdomen were studied and compared with a similar series of 346 vertical incisions recently reported from the same hospital

From the Department of Surgery, University of Michigan.

1. Baudelocque, C. A.: Nouveau procédé pour pratiquer l'opération césarienne, Thesis. Paris, no. 132, 1823.
2. Pfannenstiel, J.: Ueber die Vortheile des suprasymphysären Fascienquerschnitts für die gynäkologischen Koeliotomieen, Samml. klin. Vortr., 1900, no. 268 (Gynäk. no. 97), p. 1735.
3. Maylard, A. E.: Brit. M. J. **2**:895, 1907.
4. Boeckmann, E.: St. Paul M. J. **12**:255, 1910.
5. (*a*) Sprengel, O.: Arch. f. klin. Chir. **92**:536, 1910. (*b*) Bakes, J.: ibid. **96**:205, 1911.
6. Moschcowitz, A. V.: Ann. Surg. **64**:268, 1916.
7. Quain, E. P.: Tr. West. S. A., 1917, p. 353.
8. Moore, W. J.: Ann. Surg. **75**:70, 1922.
9. Sloan, G. A.: Surg., Gynec. & Obst. **45**:678, 1927.
10. Bartlett, W., and Bartlett, W., Jr.: Surg., Gynec. & Obst. **57**:93, 1933.
11. (*a*) Davies, F., and Wakeley, C. P. G.: Australian & New Zealand J. Surg. **2**:381, 1933. (*b*) Davies, F.; Gladstone, R. J., and Stibbe, E. P.: J. Anat. **66**:323, 1932. (*c*) McVay, C. B., and Anson, B. J.: Anat. Rec. **77**:213, 1940.

by Haight and Ransom.[12] Though the two series of operations do not represent exactly alternate cases, they nevertheless are from the same general period and in most instances were performed by the same surgeons.

ANATOMY

1. *Skin.*—Langer's lines of cleavage cross the skin of the anterior abdominal wall in a generally transverse direction. An incision paralleling these lines causes the least structural and cosmetic damage to the skin. It is recognized that the residual scarring of transverse incisions is less. Evidently, the low tension on the healing transverse incision is largely responsible for the difference.

2. *Muscles.*—The musculature of the anterior abdominal wall is composed of two groups, the "flat muscles" (the external oblique, the internal oblique and the transverse) and the rectus muscles with the variable pyramidalis muscles. The muscle and aponeurotic fibers of the first group run transversely, and the muscle fibers of the second run vertically.

The oblique muscles are fanlike structures. The external oblique takes its origin from the anterolateral aspect of the lower eight ribs. The internal oblique originates mainly from the iliac crest. Superiorly the fibers of the external oblique muscle and aponeuroses run transversely, and inferiorly they assume a progressively oblique downward course. The aponeurotic fibers of the internal oblique muscle run transversely in the lower part of the abdomen and assume a progressively oblique upward course as they extend farther up the anterior abdominal wall. At no place in the anterior wall do the fibers of either oblique muscle deviate from the horizontal by more than 30 degrees. The transverse (transversalis) muscle is truly transverse. The aponeuroses of the three "flat muscles" enclose the rectus muscle as the rectus sheath and insert in the linea alba. Therefore the strong fibers of the rectus sheath assume the same general transverse direction as the muscle fibers they represent (fig. 1).

The rectus muscle is attached above to the anterior surface of the cartilages of the fifth, sixth and seventh ribs. Its upper attachment is three times as broad as its pubic insertion. Its lateral border at the costal margin may extend laterally as far as the anterior axillary line. Its medial border is separated from its fellow of the opposite side by the linea alba. The rectus muscle has three or four transverse fibrous intersections, called "lineae transversae." One is located at or near the umbilicus, while two more are equally spaced between this intersection and the origin of the muscle. If more than three are present, the others are distributed below the umbilicus. These fibrous intersections are tightly adherent to the anterior rectus sheath and limit its retraction when sectioned (fig. 2).

An incision of the abdominal musculature that parallels all of the fleshy and aponeurotic fibers causes the least structural and physiologic damage. An incision having this characteristic can be employed only if a small incision will suffice. The McBurney incision and the transverse midabdominal incision in which neither rectus muscle is sectioned are examples of this ideal type of incision. When larger incisions are needed, it becomes almost universally necessary to cut across either heavy muscle or aponeurotic fibers. It might appear theoretically better to sacrifice the fibers of the rectus sheath in order to save the rectus muscle. However, as a result of the lateral pull of the "flat muscles," retraction of the cut edges of the rectus sheath (or of the aponeuroses of the "flat muscle") always follows a vertical incision. Sloan [9] devised a means of measuring this retraction and found that with the patient under light anesthesia a pull of 30 pounds (13.5 Kg.) was required to

12. Haight, C., and Ransom, H. K.: Ann. Surg. **114**:243, 1941.

approximate the edges of a 3 inch (7.5 cm.) vertical incision. He also noted that the force necessary for approximation increased in proportion to the square of the length of the incision. Thus, a 5 inch (12.5 cm.) vertical incision requires a pull of 80 pounds (36.5 Kg.) to effect approximation. In a vertical incision the strong fibers of the aponeuroses (or rectus sheath) are cut transversely to their long axis, and in closing such an incision the sutures will parallel rather than transect strong fibers. This becomes of importance as one realizes that at rest there is a pull across this suture line of between 30 and 80 pounds (13.6 and 36.3 Kg.) and that this pull is increased considerably if the patient coughs or retches. In many instances the suture line fails to hold and eventration occurs. This is less likely to occur, however, if the aponeuroses are incised transversely, since then practically no pull is required to approximate their edges. This results because contraction

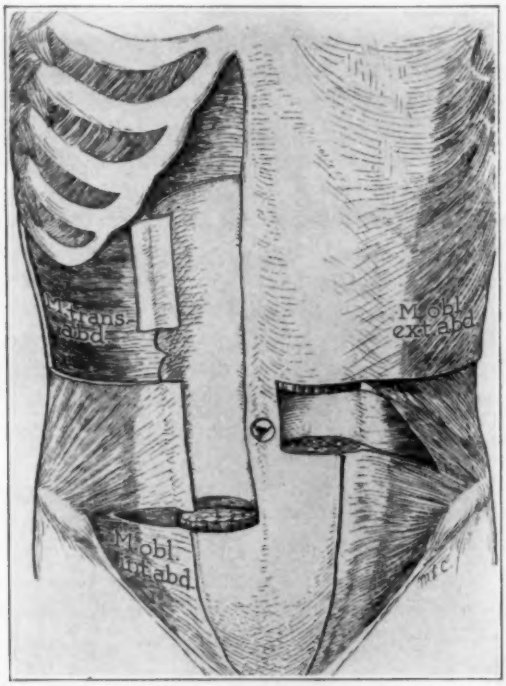

Fig. 1.—Drawing illustrating the muscles of the anterior abdominal wall and the formation of the rectus sheath from their aponeuroses. On the right is illustrated the origin of the external oblique and internal oblique muscles and the formation of the anterior rectus sheath above the linea semicircularis. The external oblique muscle contributes solely to the anterior sheath, while the internal oblique, in this location, contributes to both the anterior and the posterior sheath. In the lower left is illustrated the anterior rectus sheath below the linea semicircularis. Here the aponeuroses of the external and internal oblique muscles as well as the transverse muscle contribute to the anterior sheath. As illustrated on the left, the posterior rectus sheath is formed from part of the aponeurosis of the internal oblique muscle and from that of the transverse muscle. Note the relative transverse course of the aponeurotic fibers of the anterior abdominal muscles.

of the "flat muscles" will approximate rather than separate their own aponeurotic fibers. In addition, the closure of the transverse incision will be secure, because the sutures effecting approximation will pass across, rather than parallel, the heavy aponeurotic fibers.

Sectioning of one or both rectus muscles has no serious anatomic or physiologic sequelae. The muscles when healed will simply present an extratendinous inter-

section without functional impairment.[13] These muscles should not be sectioned injudiciously, however, since frequently a short muscle-retracting incision will suffice. In view of the apparent absence of damage following sectioning of the rectus muscle, it is doubtful if it is justifiable to subject the patient to the increased trauma and operative time required for the large muscle-retracting incisions advised by Singleton [14] and Sloan.[9]

3. *Blood Supply.*—The blood supply to the abdominal wall is abundant except at the linea alba. The main supply is derived from the superior and the inferior epigastric artery, which are branches of the internal mammary and the external iliac artery respectively. These vessels lie, for the most part, posterior to the rectus

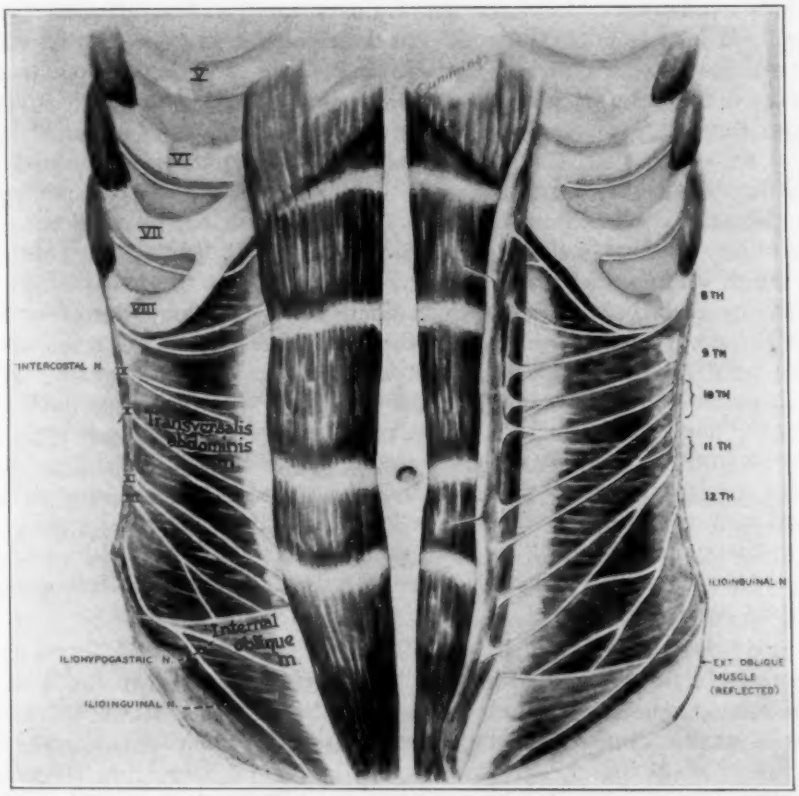

Fig. 2.—The nerves of the anterior abdominal wall and their relationship to the muscles. Note that many of the intercostal nerves are represented by more than one trunk and that there are frequent intercommunications. The rectus abdominis muscles are also shown with their transverse intersections.

muscle, where a rich anastomosis is formed. The remainder of the blood supply is derived from the deep circumflex iliac artery and from the lumbar and intercostal arteries. These also contribute to the anastomosis just mentioned. The transverse incision is undoubtedly more tedious to make, since it passes across a rich vascular bed. This same factor, however, serves to hasten healing of wounds and cannot necessarily be considered a disadvantage of the incision.

13. (*a*) Farr, R. E.: Journal-Lancet **32**:561, 1912; (*b*) in discussion on Meyer.[16] (*c*) Moschcowitz.[6]

14. Singleton, A. O.: South. Surgeon **3**:235, 1934.

4. *Innervation.*—The abdominal parietes derive their innervation from the lower six thoracic nerves and the first lumbar nerve. These nerves do not generally exist in single trunks as frequently described. Davies [11] has pointed out that the intercostal nerves, while still in the wall of the chest, exist as several branches (usually three) and not as single nerve trunks. These nerves frequently intercommunicate with neighboring intercostal nerves via a small branch that passes deep to the ribs. The intercostal nerves pass beneath the costal cartilages and enter the abdominal wall, usually as a single trunk. In the abdominal wall the nerves lie between the transverse muscle and the internal oblique muscle, where they form a free plexus.[11a] Figure 2 illustrates the actual anatomic relationship and intercommunications between the larger branches of various intercostal nerves. A more complex intercommunication between the finer nerve fibers can be demonstrated by careful dissection. It is to be noted, especially on the right side of figure 2, that a majority of the nerves are represented by several trunks. It is possible to show that any one nerve in the anterior abdominal wall contains fibers from at least two, and sometimes three, intercostal nerves.[11a] Furthermore, any one nerve at the lateral border of the rectus muscle is distributed to two segments of that muscle. Each myotonic segment is therefore supplied by at least two and possibly three, segmental nerves. This may well account for the fact that two and sometimes three intercostal nerves can be sectioned without noticeable damage.

The ninth intercostal nerves pass transversely across the abdomen at a point one third the distance between the umbilicus and the xiphoid process and this demarks the directional proclivities of the intercostal nerves. Nerves above this line tend to deviate upward, while those below deviate downward. When an incision is made lateral to the midline, the transverse variety is least likely to cause injury to the nerves. An incision in the upper part of the abdomen may be made obliquely downward and out without causing appreciable injury to nerves, while one in the lower part of the abdomen should be made obliquely upward and out. A vertical incision that passes through or laterally to the rectus muscle will enervate whatever tissue lies medially to it. As nerve tissue shows little tendency to regenerate, the enervated muscle is permanently damaged, and frequently atony and atrophy result.

TYPES OF TRANSVERSE INCISION

Variations in transverse incisions evolve principally around methods of dealing with the rectus muscles. Some (Singleton,[14] Sloan [9] and Mason [15]) have been reluctant to section even part of the rectus muscle and their incisions are directed at methods of obtaining the greatest exposure without sacrificing these muscles. Many others (Maylard,[3] Boeckmann,[4] Sprengel,[5a] Bartlett and Bartlett [10] and Moschcowitz [6]) have had no hesitancy to section the rectus muscles, and consequently their incisions are of simpler construction. In addition, many prefer to make their incisions slightly oblique rather than strictly transverse. Meyer [16] has advocated a "flap incision" with the greater part of the incision in the transverse plane.

1. *Transverse Muscle-Retracting Incision.*—In making incisions of this type efforts have been aimed at saving the integrity of the rectus muscles. Anatomically and physiologically, such an incision would appear sound. However, its construction, in general, is time-consuming, and at best exposure is limited.

15. Mason, J. T.: New Abdominal Incision, Arch. Surg. **19**:129 (July) 1929.

16. Meyer, W.: Ann. Surg. **62**:573, 1915; Rectangular Flap Incision, J. A. M. A. **69**: 1677 (Nov. 17) 1917.

Singleton [14] and Sloan [9] have strongly advised this type of incision for work in the upper part of the abdomen. Sloan incises only the posterior rectus sheath and linea alba in a transverse plane. He prefers a midline vertical skin incision through which both anterior rectus sheaths are freed. This he follows with two vertical incisions, one through each anterior rectus sheath. Through these the rectus muscles are freed from their anterior sheaths and retracted laterally. The posterior sheaths of the muscles along with the linea alba are then sectioned in a transverse plane. Singleton has improved on this incision by approaching through a transverse cutaneous incision and by sectioning one of the anterior rectus sheaths transversely. Singleton and Sloan have claimed that that exposure is adequate for the average operation on the upper part of the abdomen. Others, however, feel that the exposure obtained is still inadequate and does not justify the increase in time needed for opening and closing such an incision. When a small incision in the upper part of the abdomen will suffice, it is advisable to make a midline transverse incision of all layers except the rectus muscles and retract these as conditions warrant.

The Pfannenstiel incision is the time-honored incision for pelvic operations. Owing to the altered construction of the rectus sheath in this region, a muscle-retracting incision is easier made. The rectus muscle, usually devoid of tendinous intersections in this region, is easily freed and retracted. Posteriorly, there is no true rectus sheath, only condensed properitoneal fat and peritoneum,[11c] and this can readily be opened in any direction. If exposure is inadequate the rectus muscles can be sectioned without danger, preferably near their pelvic attachment, as advised by Cherney.[17] If the incision is carried far laterally, it should be made obliquely upward and out along the course of the external oblique muscle. With a little care, the inferior epigastric vessels can be avoided.

2. *Direct Transverse Incision of All Layers.*—This is the incision of choice with most advocates of transverse incision. Those who oppose it do so usually on the grounds that it permanently injures the rectus muscle. It appears doubtful that this accusation is justifiable, since the literature is wanting in instances in which functional or anatomic impairment has resulted from transverse sectioning of the rectus muscles. Among those who have investigated this question, there is agreement that when healed the rectus muscle simply presents an extratendinous intersection without further damage. Farr [13a] queried 30 users of transverse incision and was unable to locate a single incidence of sequelae directly resulting from sectioning of the rectus muscle. Among those who section the rectus muscle, there is also agreement to the fact that, if necessary, both rectus muscles can be sectioned without harm.

A transverse incision of this type may be made at any place over the anterior abdominal wall, though the site of election for laparotomy is usually 3 to 5 cm. above or below the umbilicus.[18] A left-sided infraumbilical transverse incision gives excellent exposure to the sigmoid colon. For the upper part of the abdomen, Bailey [19] prefers to use the ninth rib as a landmark and carries his incision entirely across the abdomen from one costal arch to the other. More commonly the incision is started just laterally to the midline and carried to the opposite costal arch. Depending on the needs, the incision may pass through one or both anterior rectus sheaths. The peritoneal cavity can now be opened through the linea alba and the round ligament of the liver ligated and sectioned. Moschcowitz [6] and others have preferred to place hemostatic mattress sutures through the rectus muscle and rectus

17. Cherney, L. S.: Surg., Gynec. & Obst. **72**:92, 1941.

18. Gurd, F. B.: Canad. M. A. J. **42**:10, 1940. Bartlett and Bartlett.[10] Moschcowitz.[6]

19. Bailey, H.: Tr. Internat. Coll. Surgeons **1**:158, 1938.

sheaths before sectioning the former. This, however, is not necessary, since the amount of bleeding is variable and can be controlled readily at the time of sectioning. Bleeding should be controlled by suture ligatures preferably incorporating a small piece of the rectus sheath, because ligatures or even suture ligatures will easily pull from muscular tissue. The peritoneal cavity can now be opened throughout the length of the incision. If the patient is hyperextended by means of a lift or by hyperextending the table, good exposure is afforded with a minimal amount of retraction. Closure of such an incision is greatly facilitated by flexing the patient. If this is done the incisional edge will approximate without tension. The first layer of sutures can be of chromicized catgut or interrupted black silk or cotton. It will approximate the peritoneum and the posterior rectus sheath, and where the incision extends far laterally it may approximate the peritoneum and the transverse abdominal muscle. Suturing of the rectus muscle is not only difficult and unsatisfactory but entirely unnecessary. When the anterior rectus sheath is approximated, the edges of the muscle will be in close proximity. The anterior rectus sheath should be closed with a nonabsorbable suture material, such as fine steel wire, cotton or silk. The muscle and aponeurotic layers lateral to the sheath should be closed with either fine cotton or silk. The subcutaneous tissue and skin can also be closed with fine silk or cotton. Recently we have been using two or three subcuticular steel wire sutures. These have been removed on the eighth or ninth day, and have given excellent results. Where drainage is indicated, it can be accomplished through the lateral borders of the incision. Retention sutures are unnecessary, but one may place reenforcing sutures through the linea alba, as this section of the incision will heal most slowly because of its poorer blood supply. The Bartletts [10] prefer to stagger the various layers of the abdominal wall as they are incised and have contended that a stronger closure is effected if the sutured layers are not all in the same plane of section. It is questionable whether this slight increase in strength justifies the extra time required.

3. *Oblique Incision.*—When there is a narrow costal arch, access to the upper part of the abdomen can be facilitated by using an oblique incision. The obliquity can be varied to meet the needs at hand, but the nearer it approaches the transverse plane the better will be its structure and its physiologic qualities. An incision of the Kocher type, which lies close to and parallel to the costal arch, is to be condemned, because it sections too many nerves. All layers of the abdominal wall may be sectioned in the plane of the cutaneous incision, but a stronger closure is possible if the two oblique muscles lateral to the rectus sheath are sectioned along the course of their fibers. Singleton [20] has advised an oblique lateral abdominal incision in which the rectus muscle is retracted medially. His incision extends from a point 3 to 4 inches (7.5 to 10 cm.) above the umbilicus down to a point just posterior to the anterior superior spine of the ilium and slightly above the iliac crest. The rectus muscle is freed and retracted medially. Such an incision undoubtedly sections the ninth, tenth and eleventh intercostal nerves and for that reason cannot be favored for general usage. If the rectus muscle were sectioned adequate exposure could be obtained through its medial portion without carrying the incision far into the flank; thus its chief drawback would be avoided. An oblique incision affords unusually good exposure of the biliary system with the least amount of retraction. A similar incision on the left gives equally good access to the spleen, and if it is extended to include part of the right anterior and posterior rectus sheaths good access is afforded to the stomach also. An oblique incision in

20. Singleton, A. O., and Blocker, T. G., Jr.: Problem of Disruption of Abdominal Wounds and Postoperative Hernia, J. A. M. A. **112**:123 (Jan. 14) 1939.

the lower part of the abdomen should follow the fibers of the external oblique muscle or aponeuroses; such an incision affords good exposure to peritoneal as well as extraperitoneal structures located in this region. The suprapubic curvilinear incision as used by Judd has proved to be an excellent incision for repair of bilateral inguinal hernias (fig. 3).

4. *Flap Incision.*—Meyer,[16] who was a strong advocate of transverse incisions, pointed out that when exposure proves inadequate with a transverse incision an extension can be carried either up or down in the medial portion of the rectus sheath, thus making a rectangular flap. This procedure can be used in place of an oblique incision when the costal arches are steep. The longitudinal portion of the incision should be as short as possible, since this is its weakest part. A flap incision

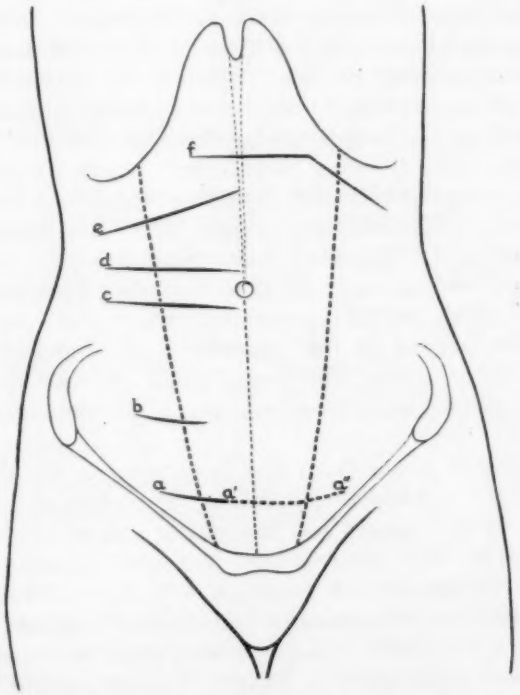

Fig. 3.—Common locations for transverse incision: *a–a'*, unilateral inguinal herniorrhaphy incision; *a–a''*, incision used for bilateral inguinal herniorrhaphy; *b*, Davies[11a,b] or Rockey (*S. Clin. North America* **4**:1205, 1924) appendectomy incision; *c*, laparotomy incision especially valuable in cases of intestinal obstruction (similar incision on the left gives good exposure of sigmoid colon); *d*, incision used for right colectomy; *e*, incision giving good access to biliary system (similar incision on the left used for splenectomy); *f*, incision used for gastric operations.

is more difficult to close than a strictly transverse or oblique type, and this difficulty increases as the longitudinal portion lengthens. The possibility of a "flap incision" should nevertheless be kept in mind, since it frequently proves a helpful adjunct to a transverse incision.

CLINICAL ADVANTAGES OF THE TRANSVERSE INCISION

Complications of laparotomy, such as evisceration, incisional hernia and abdominal adhesions, frequently constitute a more serious and difficult problem than the original operation. Singleton[20] in an exhaustive survey reported disruption

to have a frequency varying from 0.6 to 3 per cent and to carry a mortality of between 25 and 40 per cent. (Others list mortality rates as high as 75 per cent.) In 3,147 anatomic incisions (transverse or oblique) he found only 1 disruption, or an incidence of 0.03 per cent.

In an even greater number of incisions, disruption starts in the deeper layers but fails to be complete, and an incisional herniation develops. Sloan,[9] investigating vertical incisions, found that of those 5 inches (12.5 cm.) or more in length and of ten years' duration, 80 per cent showed evidence of herniation or weakness. A survey of the literature reveals an incidence of postoperative incisional hernias of from 2 to 10 per cent. Mason,[15] reporting on a large series from the Mayo Clinic, showed that 10.8 per cent of all herniorrhaphies were done to repair abdominal incision. This is of greater significance as one realizes that many incisional hernias go unrepaired and even undiagnosed. Incisional hernias are rare in transverse incisions, and the few that do occur are almost universally the end results of a badly infected incision. Coryllos, as quoted by Farr,[13a] studied 2,855 transverse incisions and found only 7 postoperative hernias, not one of which followed primary healing. This gave an incidence of 0.27 per cent in the cases in which there was suppuration and none in the cases of clean wounds. Similar results were found on analyzing 1,542 cases, including some of those reported by the more recent advocates (Moschcowitz,[6] Wanscher,[21] Boeckmann,[4] Hesselgrave,[22] Sprengel,[5a] Lynn and Hull,[23] Saunders [24] and Singleton [20]). In this series only 2 hernias were reported, both in badly infected wounds. This gives an incidence of only 0.13 per cent. With the 225 consecutive transverse incisions in the upper part of the abdomen studied at the University of Michigan Hospital, only 1 herniation was encountered, and this was a small omental hernia at the site of drainage. It had no clinical significance and was found only after careful check-up examination.

This low incidence of evisceration and herniation is the direct result of the stronger closure effected in transverse incision. The edges of a transverse incision tend to approximate by themselves, and the sutures that effect this closure insure a firmer incision because they transect the stronger aponeurotic fibers of the abdominal wall. In closing vertical incisions difficulty is frequently encountered in closing the peritoneum and the posterior rectus sheath. Weakness of this closure, aside from favoring evisceration and herniation, also serves as a nidus for the development of abdominal adhesions. As many [25] have pointed out, adhesions are less frequent in transverse incisions. The value of this is better appreciated when it is realized that adhesions are the most common causative agents of acute intestinal obstruction and that this condition carries a mortality rate of about 26 per cent.[26] Aside from this, countless other patients present minor complaints which are generally assumed to be the result of adhesions.

Pulmonary atelectasis and pneumonia remain the most important causes of early postoperative complications. Especially is this so with operations on the upper part of the abdomen, which have these complications in from 5 to 12 per cent of the cases.[27] With the series of transverse incisions in the upper part of the abdomen

21. Wanscher, O., cited by Boeckmann.[4]
22. Hesselgrave, S. S.: St. Paul M. J. **12**:531, 1910.
23. Lynn, F. S., and Hull, H. C.: Ann. Surg. **104**:233, 1936.
24. Saunders, R. L.: South. Surgeon **6**:365, 1937.
25. McArthur, L. L.: Surg., Gynec. & Obst. **20**:83, 1915. Farr.[13a,b] Moore.[8]
26. Boyce, F. F., and McFetridge, B. M.: South. Surgeon **6**:109, 1937.
27. Jones, D. F., and McClure, W. L.: Surg., Gynec. & Obst. **51**:208, 1930.

studied at the University of Michigan Hospital, there were no deaths attributable to pulmonary complications, and the incidence of these complications was only 2.6 per cent (table). This low percentage is of greater significance if compared with the incidence of 9.5 per cent for vertical incisions as reported by Haight and Ransom [12] from the same hospital. In a similar series of 125 cases reported by Jones and McClure [27] there were no cases of atelectasis or pneumonia, but there were 5 cases of pulmonary emboli, 2 of which were fatal. Haight and Ransom [12] have pointed out that decreased respiratory and cough efficiency are important causative factors of these complications. A vertical incision passing through or laterally to a rectus muscle will injure the intercostal nerves to that region. These sectioned nerves are hyperirritable during the early postoperative course. In the patient's subconscious effort to minimize pain, the abdomen is splinted. As a consequence, diaphragmatic excursions are impaired, and a decrease in vital capacity and tidal air results. Beecher [28] has reported this reduction to be as much as 58 per cent. This decreased ventilation favors the development of anoxia and patchy atelectasis (postoperative bronchopneumonia). Also when a vertical incision has been used coughing not only endangers the incision but is very painful. This is

Comparative Study of Pulmonary Complications Following Transverse and Vertical Incisions

	Type of Incision	
	Transverse	Vertical
Number of cases	225	346
Patchy atelectasis	5 (2.2%)	26 (7.5%)
Massive atelectasis	0	5
Pleuritis	0	1
Infarct or embolism	1	1
Total pulmonary complications	6 (2.6%)	33 (9.5%)
Pulmonary complications chief cause of death	0	3
Pulmonary complications contributing cause of death	0	1

important in view of the fact that coughing has proved to be one of the most important physical means of preventing postoperative complications. The reduction of postoperative pain and the stronger closure afforded by transverse incisions, aside from being heartily welcomed by the patient, allow for earlier and greater activity with resulting reduction in pulmonary hypostasis. This reduction of hypostasis, along with the betterment of the respiratory and cough efficiency, serves to retard the incidence of pulmonary complications.

Transverse incision in many instances allows for better and easier exposure. This is especially so in operations on the gallbladder, because the incision approaches the operative field more directly. For operations on the upper part of the abdomen a transverse incision need not extend into that portion of the celomic cavity where the greater portion of the small intestine lies. This practically eliminates this structure from the operative field. Thus easy exposure is accomplished without repeated packing and manipulation of the small intestine. Hyperextension of the patient will further aid exposure and facilitate operation. This helps reduce trauma and favors a smoother postoperative course. The little extra time needed to make transverse incisions is usually more than offset by that ultimately saved as a result of improved exposure.

28. Beecher, H. K.: J. Clin. Investigation **12**:639, 1933.

The narrow, firm cicatrix, the reduction of postoperative pain, the absence of incisional neuromas [29] and the shorter period of hospitalization are all factors greatly appreciated by the patient. A patient with a transverse incision can, if conditions warrant, be allowed up with relative safety almost as soon as he has recovered from the anesthetic. Usually, however, a patient who has had an operation on the upper part of the abdomen is not allowed out of bed until the seventh postoperative day. This reduces the average hospitalization period, as required with vertical incision, by five to ten days. A person requiring operation should be entitled to every comfort compatible with good therapy, and in the case of abdominal operation it would seem that frequently this can best be accomplished through the use of a transverse abdominal incision.

SUMMARY

The transverse abdominal incision is based on sound anatomic, physiologic, and clinical principles. This incision parallels the lines of skin cleavage, the heavier muscular and aponeurotic fibers and the greater portion of the nerves of the anterior abdominal wall. As a result of the stronger incisional closure thus afforded, there are fewer eviscerations, herniations and abdominal adhesions.

The incidence of pulmonary complications found after 225 consecutive transverse incisions in the upper part of the abdomen was 2.6 per cent, which is considerably below the 9.5 per cent for a comparable series of vertical incisions.

The virtual absence of incisional pain, the narrow, firm cicatrix and the average reduction of from five to ten days in the period of hospitalization are attributes of the transverse incision worthy of consideration.

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29. Bancroft, F. W.: Painful Postoperative Abdominal Scars, Arch. Surg. **21**:289 (Aug.) 1930.

PRIMARY INTRACRANIAL LYMPHOSARCOMA

A REPORT OF TWO CASES AND REVIEW OF THE LITERATURE

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In the past half-century pathologists have learned to recognize tumors arising from lymph nodes and other lymphatic structures in nearly every organ and structure of the body; however, so far as we can determine, the skull and intracranial dura mater have not been indicated as the primary site of origin of lymphosarcoma.[1] Therefore, there is adequate cause for reporting 2 cases in which the primary focus appears to have been in the intracranial dura mater or possibly in the overlying cranial bone.

REPORT OF CASES

CASE 1.—A white man, aged 24 years, came to the Mayo Clinic in August 1926, because of symptoms of an intracranial lesion. Two years before this, he had been struck by a baseball in the right parietal region but had not lost consciousness. There were no symptoms from this nor any other symptoms until four months before the patient came to the clinic, at which time he noticed a small, hard lump at the site of the old injury. Although there was a slowly progressive increase in the size of this tumefaction, constant severe frontal headaches began only two weeks before his registration. These bouts of headache were followed by attacks of motor and sensory paresis of the left hand, progressing up the arm into the left side of the face and chest. In addition, there had been several similar attacks with "thickness of speech." Severe vomiting had occurred during the previous two days.

A thorough physical examination did not disclose any infectious process or neoplasm elsewhere in the body. The neurologic examination revealed cloudiness of the sensorium, so that the patient was mentally dull and confused. There was evident central paresis of the left half of the face and the left upper extremity. Examination of the scalp disclosed the swelling in the right midparietal region to be tender, smooth, firm and not movable with the scalp. It was elevated about 1 cm. and was about 3 to 4 cm. in diameter. A meningioma with hyperostosis in the right parietotemporal area was suspected, although roentgenograms of the head were reported not to show evidence of it and recent review of them has confirmed this.[2]

Exploratory craniotomy was performed a few days after the patient's admission to the hospital. The operation disclosed a malignant tumor arising from the dura (9 by 8 by 3 cm.), eroding it and the overlying portion of the skull (5 by 4 by 8 cm.) on the right side. After removal of most of the tumor, a wide gap in the skull was left and the wound closed. The patient survived the operation for nine days, having slowly failed, with hyperthermia and tachycardia.

Section on Neurologic Surgery of the Mayo Clinic.

Abridgment of part of a thesis submitted by Dr. Abbott to the Faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of M.S. in Neurosurgery.

1. We are familiar with lymphosarcoma whose primary focus is within the orbit and which by subsequent extension comes to involve the intracranial dura mater, but it is not our purpose to discuss this problem. It is our impression that the primary symptoms produced by this and other forms of sarcoma of the orbit are referable to the involved orbit and that these forms of sarcoma can be diagnosed as such; thus, they need not be confused with the type here under consideration.

2. Roentgenograms of the preserved bone flap were made recently and disclosed only slight evidence of the infiltrative process.

A complete necropsy, performed two and a half hours after death, was permitted, which, aside from the intracranial lesion, disclosed minimal lesions of both healed and active pulmonary tuberculosis, which would have been difficult to ascertain clinically. Also there were horseshoe kidneys, leukoplakia of the esophagus and mild (benign) hyperplasia of the lymph follicles of the intestine.

Examination of the intracranial dura mater revealed the operative defect to be surrounded by an irregular rim of tumorous tissue 2 to 5 cm. wide. On gross inspection this was identical with the operative specimen, although not as thick.

Microscopic study of sections made from the tumorous mass in the dura mater showed that it was partially surrounded by a fibrous capsule, thin strands of which extended down into it and by branching formed a fibrous trabecular framework. It was an extremely cellular tumor composed principally of two types of cells; those most abundant were small lymphocytes that had hyperchromatic nuclei and scanty cytoplasm and whose outlines were not too well defined. Nucleoli were present in many, but not all, of the nuclei. There were a great many mitoses throughout the neoplasm, which added to its highly malignant character. About a third of the cells had larger, pale-staining, irregular and indented nuclei with cytoplasm varying in amount and occasionally without discernible cell boundaries. The

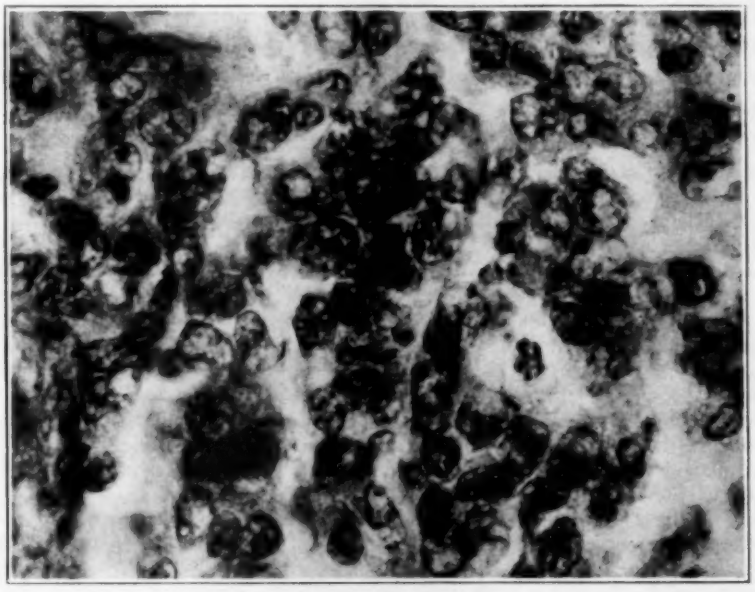

Fig. 1 (case 1).—Lymphosarcomatous cells (hematoxylin and eosin × 900).

chromatin appeared in these to be collected in fine strands and minute dots, and nucleoli of varying sizes were found more frequently than in the first type but in no constant position in the nucleus. Mitoses, although present, were not as frequent as in the smaller, darker, lymphocyte-like cells (fig. 1).

There were occasional large (giant) cells, usually stained very pale, appearing as distinct, dark, thin rims (nucleus) with fine strands of chromatin extending toward the center. An eccentric nucleolus could be seen occasionally inside these huge giant cells. Fairly frequently thin rims of irregular cytoplasm, at times of stellate outline, were encountered. These, as well as the previously described pale cells, were taken to represent the so-called reticulum cells seen in normal lymphatic structures, which here had entered into the formation of the tumor to a minor degree.

The silver-impregnated sections were not of additional aid except in detecting reticulin, which was present along the blood vessels, in the connective tissue trabecula dispersed through the tumor and also as fine intercellular fibrils. Glial cells, nerve cells or their processes were not present in any of the sections.

Sections taken through the underlying leptomeninges and cortex were of interest in that the subarachnoid space was filled with the small lymphocyte-like cells and the pia and arach-

noid were likewise infiltrated. The vessels, where pulled away from the surrounding structure, were covered with a layer of these cells and could be followed for 2 to 3 mm. on into the cortex in the pial funnel and Virchow-Robin spaces; here they appeared as well formed perivascular cuffs without invading the nerve tissue (fig. 2). This was obviously an infiltration process and not a primary propagation, such as is seen in the perivascular sarcomas.

There were minor changes in the nerve tissue subjacent to the tumor as evidenced by a minor degree of gliosis and edema (gemästete glia cells; swollen and increased numbers of oligodendroglia and microglia cells).

The infiltrative process in the bone was entirely osteoclastic; thus the small hyperchromatic cells were present in the haversian canals and in lacunas and irregular eroded channels. Although the skull was thickened, there were but few tumor cells exterior to the outer table. The greatest erosion was of the inner table, as though the neoplasm had originated in the dura and extended into the overlying portion of the skull (fig. 3*a*).

A diagnosis of lymphosarcoma involving the dura mater, skull and leptomeninges with perivascular cortical invasion was made. The possibility of this tumor's being Hodgkin's disease was ruled out by the absence of Dorothy Reed cells and other evidences of Hodgkin's disease.

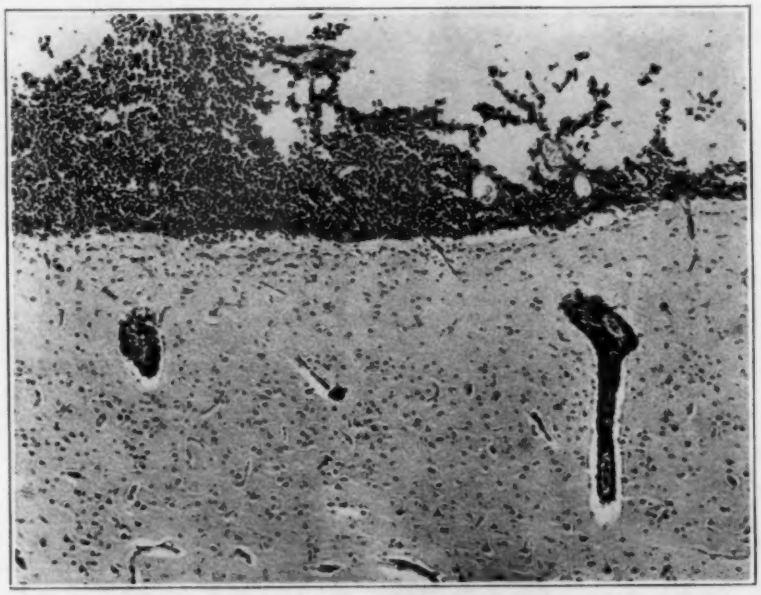

Fig. 2 (case 1).—Lymphosarcoma in the subarachnoid space and extending into the brain by means of the perivascular spaces (hematoxylin and eosin × 55).

Comment on Case 1.—The question in this case is not of the identity of the tumor or the possibility of metastasis; both are well answered in the thorough necropsy and study of the sections which identified the growth as a lymphosarcoma without any evidence of tumor elsewhere in the body. The question is: Did the tumor arise in the skull or in the dura mater? This can be answered partially by pointing to the erosion of the inner table as compared with the minor involvement of the outer table and the presence of the major part of the tumor in the dura mater. It is recognized that the dura mater does not contain any lymphatic structures. The same is, of course, true of the leptomeninges and the nervous system; however, it may or may not be of significance to point out that any infection or injury does call forth an abundance of lymphocytes into the injured dura mater. This patient did have a previous injury to the skull, although of a minor nature. If one may theorize, might it be possible that a focus of lymphocytes in the dura mater was

thus formed from which the neoplasm may, in some unknown manner, have become malignant? Nevertheless, the possible origin in the skull itself cannot be disregarded; neither can it be proved. Such seems to have been the situation in the case reported by Bassoe,[3] except that the tumor was obviously metastatic. In discussing this case, Phemister suggested that the tumor metastasized to the skull and then extended into the dura mater, but he noted the extensive erosion of the inner table and mentioned that metastasis to the dura and subsequent infiltration of the overlying bone seemed more probable. With essentially the same reasoning, one may well argue that the tumor in case 1 originated in the dura mater and spread into the skull.

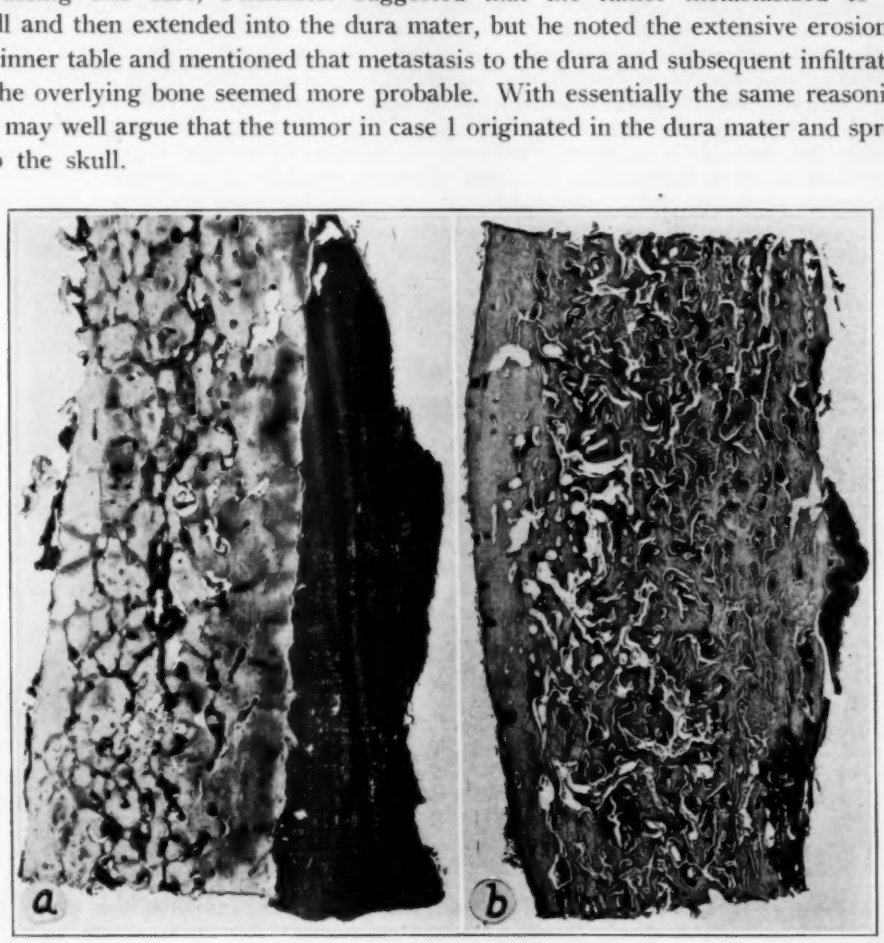

Fig. 3.—Lymphosarcoma involving skull and dura mater. Sections of skull: *a*, case 1, and *b*, case 2. Note erosion of inner table and presence of tumorous mass in both *a* and *b*; however, in *a* the outer table also is slightly involved with a few small tags of tumor present in the subaponeurotic region. It is not certain whether the primary site was in the dura mater or in the skull (hematoxylin and eosin × 5½).

The following case is similar to case 1 but regrettably necropsy was not obtained. Nevertheless, since the case is so unusual and of equal importance, it is here described.

Case 2.—A white woman, aged 57 years, registered at the clinic on Feb. 3, 1926, complaining of malaise, anorexia, dizziness, headaches and difficulty in walking, which had been present since May 1925. Roaring in the ears, mostly on the right, on lying down had begun in October. About six months previous to her entry at the clinic, she had noted a persistent "lump" in the left frontoparietal region. For four months, numbness and paresthesias of

3. Bassoe, P.: Tumor-Like Infiltration of Cerebral Dura: A Case of Lymphosarcoma with Clinical Picture of Hodgkin's Disease, Arch. Neurol. & Psychiat. **7**:788-790 (June) 1922.

the right finger tips had been noted, but previous to this (since November 1925) she had had monthly attacks of paresthesias of the right finger tips, lasting from fifteen to twenty minutes. Vision had been poor for two months and the defect had been associated for six to eight weeks with diplopia.

The examination revealed a somewhat confused middle-aged patient who had moderate arteriosclerosis but was without neurologic lateralizing signs. The swelling in the left frontoparietal region of the scalp was only slightly tender, firm and rounded (dome-shaped) and seemed attached to the skull. It was elevated about 1 cm. and was 3 or 4 cm. in diameter. The spinal fluid gave positive Wassermann and Nonne reactions. A diagnosis of syphilis of the central nervous system was made, and appropriate treatment instituted. The tumefaction in the frontoparietal region of the scalp was taken at first to be a gumma, but it did not respond to antisyphilitic treatment; thereupon an osteomatous nature was assumed (on roentgenographic interpretation) and the patient was allowed to go home, with instructions to return to the clinic in September of the same year.

On the patient's return there was evidence of an increased intracranial pressure, and, in view of the mass in the left frontoparietal region of the scalp, a flap was turned down over this area on Oct. 6, 1926. An osteomatous nodule was found adherent to the dura. On the medial aspect of the dura at this point was an extensive mushroom-like neoplasm extending out over the temporoparietal area. A portion of the tumor and of the bone flap was removed. Postoperatively, roentgen therapy was administered, with some improvement of the patient's symptoms.

The surgical specimen was reported as chronic inflammatory tissue, and it was not until the patient returned, in December 1927, because of left cervical adenopathy which definitely appeared to be extending down through the scalp from the operative site into the cervical chain of lymph nodes, that the correct diagnosis was made by means of removal of a cervical lymph node for biopsy. Subsequently, heavy roentgen therapy to the glands of the neck and the cerebral lesion relieved the most distressing lymphedema of the left side of the face.

The patient returned to the clinic on Oct. 24, 1928, because of a gradual return of the "lump in the neck," edema of the left side of the face and bulging in the cranial decompression wound. Examination substantiated her observations and also disclosed numerous tiny shotlike lymph nodes in both sides of the neck. More roentgen therapy was instituted and she again showed some improvement. She returned home and was not heard of until by chance her death was reported. Death occurred on Oct. 25, 1932, about six years after her operation. This was confirmed by her family physician.

Sections were made of the tumorous mass, including the grossly infiltrated bone flap, and were stained with hematoxylin and eosin and by Mallory's phosphotungstic acid and Perdrau's silver impregnation methods.

Histologic investigations disclosed that the cells comprising this tumor were of three types, not including the occasional giant cells to be mentioned later. The majority were ovoid to polyhedral; they possessed a scant to moderate amount of bluish to pink-staining cytoplasm. The nuclei, although somewhat vascular, contained more chromatin than those of ordinary lymphocytes and rarely contained visible nucleoli. Cellular pleomorphism was only moderate, and mitoses were not overly abundant. Tumor giant cells were rarely encountered but when present contained single, bulky, hyperchromatic nuclei, in most cases filling nearly all of the cell. Cells of a second type, considerably larger than the cells of the small lymphocytic type, were present but fewer than the others and were characterized by their much lighter staining, indented or kidney bean–shaped nuclei containing only tiny rods of chromatin; their cytoplasm stained much lighter and its bounds were at times indistinct. These probably represented the reticulum cells and were scattered among the tumor cells without any definite pattern or evidence of their function, or evidence of their playing the major role in the formation of this tumor. They were, however, a little more numerous than in normal lymph structures. Cells of the third type appeared to be the fibroblasts and were present in the fibrous trabecula of the neoplasm.

Reticulin was demonstrated intercellularly and independent of cellular arrangement and in the fibrous trabecula. Collagen was in the bands and strands which made up the stroma of connective tissue.

The giant cells were not of the Dorothy Reed type and there were no eosinophils present; therefore, this was not Hodgkin's disease. Neither was there evidence of syphilitic gummas from which a lymphosarcoma might have arisen.

The decalcified sections made of the infiltrated bone flap disclosed that its moth-eaten appearance was due to tumor tissue infiltrating in the haversian canals and in newly formed channels resulting from an osteoclastic process (figs. 3*b* and 4*a* and *b*). The lymphosar-

comatous cells were thus present in the outer table of the skull, and a very few were situated subperiosteally. The greatest degree of destruction was on the inner surface. Reticulum cells were distributed among the smaller lymphocytic type of cells in about the same frequency as in the intracranial portion of the tumor. The infiltrative process was entirely osteoclastic; there was no evidence of any osteoblastic activity. A diagnosis of lymphosarcoma involving the skull, dura mater, leptomeninges and brain was made.

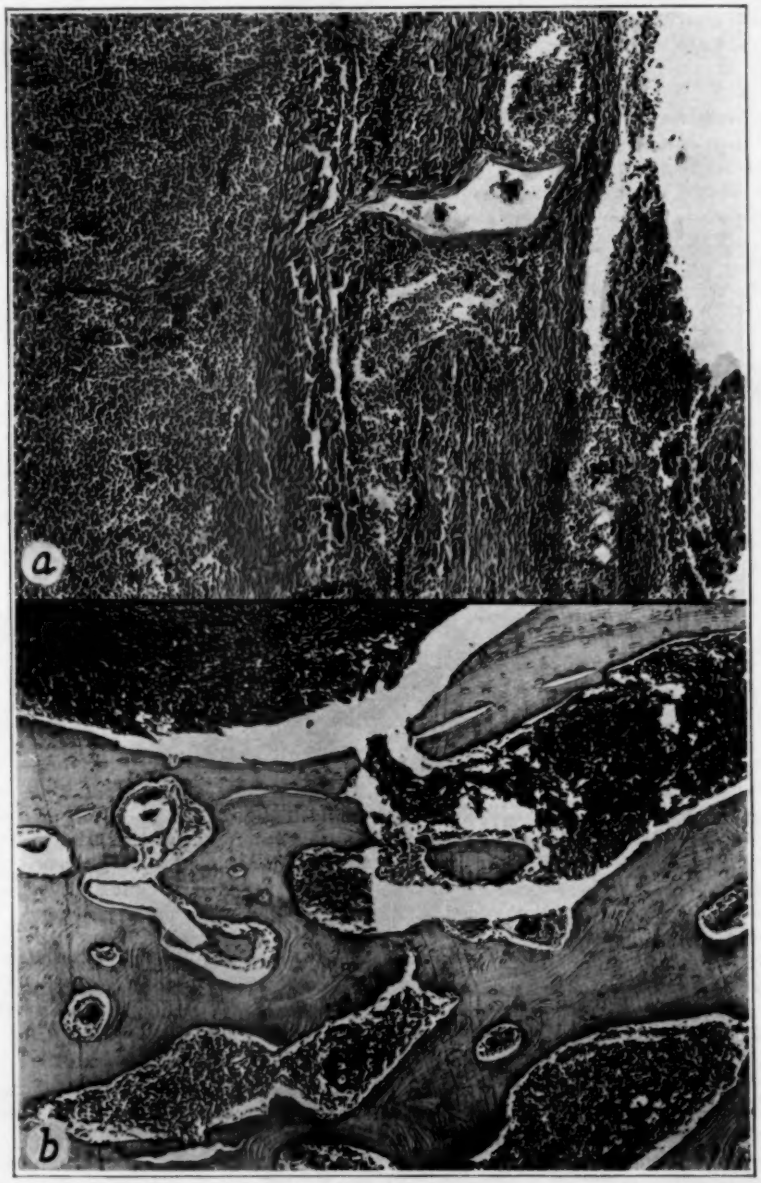

Fig. 4 (case 2).—Lymphosarcoma—small cell type. In *a*, tumor cells have infiltrated the dura mater and are seen on both its internal and its external surface (hematoxylin and eosin × 65). In *b* is shown involvement of the skull. Tumor cells are present in the haversian canals and in newly formed channels resulting from an osteoclastic process. The tumorous mass seen at the right was continuous with the intracranial (dura) tumorous mass (hematoxylin and eosin × 60).

Comment on Case 2.—From the microscopic study there was no definite evidence of the origin of this neoplasm, but in view of the greater erosion of the inner table and the presence of a large dural mass which infiltrated the brain, the evidence appeared to be in favor of its dural origin. Numerous repeated examinations had failed to show evidence of any primary lesion outside of the dura and skull. The spread of metastatic growths was seen to come from the operative site downward into the cervical lymph nodes. Thus this neoplasm appears to have been primary in the dura mater or the skull.

GENERAL COMMENT

Undoubtedly Virchow [4] had a fair comprehension of the lymphomas and lymphoblastomas and probably of lymphosarcoma, as can be discerned from the excellent description given in his "Die krankhaften Geschwülste" in 1863. However, it remained for Dreschfeld [5] in 1891 and Kundrat [6] in 1893 to identify one malignant type clearly. Kundrat chose to call this type "lymphosarkomatosis." Following this, other tumors of the lymphatic structures were recognized by Becker [7] in 1901 (giant follicular hyperplasia [8]—Brill-Symmers' disease), by Ciaccio,[9] by Goormaghtigh,[10] by Oberling [11] (reticulum cell sarcoma), by Parker and Jackson [12] and by Edwards [13] (reticulum cell sarcoma of bone). Prior to these disclosures Hodgkin's disease became well known, and its involvement of the nervous system was recognized by Murchison and others.[14] Yet after at least a half a century the etiology of these neoplasias remains obscure.

4. Virchow, R.: Die krankhaften Geschwülste, Berlin, A. Hirschwald, 1863, vol. 1, p. 543.

5. Dreschfeld, J.: Ein Beitrag zur Lehre von den Lymphosarkomen, Deutsche med. Wchnschr. **17**:1175-1177 (Oct. 13) 1891.

6. Kundrat: Ueber Lympho-Sarkomatosis, Wien. klin. Wchnschr. **6**:211-213 (March 23); 234-239 (March 30) 1893.

7. Becker, E.: Ein Beitrag zur Lehre von den Lymphomen, Deutsche med. Wchnschr. 27:726-728 (Oct. 17) 1901.

8. Brill, N. E.; Baehr, G., and Rosenthal, N.: Generalized Giant Lymph Follicle Hyperplasia of Lymph Nodes and Spleen: A Hitherto Undescribed Type, J. A. M. A. 84:668-671 (Feb. 28) 1925. Symmers, D.: Follicular Lymphadenopathy with Splenomegaly: A Newly Recognized Disease of the Lymphatic System, Arch. Path. **3**:816-820 (May) 1927.

9. Ciaccio, C.: Ueber einen Fall von Synzytium-Endotheliom der Lymphdrüsen mit Studien und Betrachtungen über die Endothelien und Endotheliome der Lymphorgane, Virchows Arch. f. path. Anat. **198**:422-448 (Dec. 4) 1909.

10. Goormaghtigh, N.: Sur la prolifération maligne du tissu réticulo-endothélial des ganglions lymphatiques, Compt. rend. Soc. de biol. **92**:457-458 (Feb. 20) 1925.

11. Oberling, C.: Les réticulosarcomes et les réticulo-endothéliosarcomes de la moelle osseuse (sarcomes d'Ewing), Bull. Assoc. franç. p. l'étude du cancer **17**:259-296 (May) 1928.

12. Parker, F., Jr., and Jackson, H., Jr.: Primary Reticulum Cell Sarcoma of Bone; Surg., Gynec. & Obst. **68**:45-53 (Jan.) 1939.

13. Edwards, J. E.: Primary Reticulum Cell Sarcoma of the Spine: Report of a Case with Autopsy, Am. J. Path. **16**:835-844 (Nov.) 1940.

14. C. Murchison (Case of "Lymphadenoma" of the Lymphatic System, Liver, Lungs, Heart and Dura Mater, Tr. Path. Soc. London **31**:372-389, 1869-1870) was the first to describe the involvement of the intracranial dura mater by a lymphoblastoma, but his patient probably had Hodgkin's disease rather than lymphosarcoma. The same is true of the lymphomatous growth in the dura with erosion of the base of the skull reported by Roncalli in 1892 (Roncalli, F.: Sarkom des Nasenrachenraumes, 1 Fall, Jahresb. ü. d. chir. Abt. d. Spit. in Basel, 1894, p. 19). Guillain, Alajouanine and Périsson (Lymphosarcome extra-dural métastatique ayant déterminé une compression médullaire d'apparence primitive, d'évolution rapidement progressive; laminectomie; extirpation et radiothérapie; guérison, Bull. et mém. Soc. méd. d. hôp. de Paris **49**:1057-1061, 1925) in 1925 claimed to be the first to report involvement in the spinal cord (dura) by lymphosarcoma. Jacod's studies in 1914 (Jacod, M.: Sur les sarcomes de la trompe d'Eustache cartilagineuse, Rev. de laryng. **2**:169-179, 1914) and later are also of importance, since they pertained to lymphosarcoma at the base of the skull.

Involvement of the nervous system by lymphosarcoma has been described by many writers but always as a metastatic or direct spread from nearby structures. In lymphosarcoma in the head, the structures at or near the base of the skull are frequently the site of origin. Sugarbaker and Craver,[15] in analyzing the records of 196 cases in which the diagnosis was confirmed by biopsy, found that in approximately two thirds of their cases the lesion began in lymph nodes and in a third it was of extranodal origin; in two thirds (65 per cent) of the latter group the initial lesion was in the "head structures" [16] but outside the cranial vault. Of the 196 cases there were only 4 instances of involvement of central nervous system tissue (brain, 1 case; spinal cord, 3).

A survey of the literature pertaining to lymphosarcoma, however, reveals a much greater frequency of neurologic symptoms than the foregoing statistics indicate;[17] a few of the reports seem worthy of review here. As far as we are aware, Woltman [18] was the first to review the literature and report a fair-sized series in which there were intracranial complications of lymphosarcoma;[19] however, previous to his report and since then many casual reports of involvement of the central nervous system and the cranial nerves have appeared. In tabulating the neurologic manifestations, it is apparent that they can be divided into the following anatomic groups: (1) extracranial or subcranial, (2) intracranial and (3) intraspinal (dura mater). We are here concerned only with the first two groups.

The first group is of interest in that the cranial nerves, making their exit through the basilar foramens, may be interrupted by pressure or by invasion of tumor cells. The majority of the observations fall into this group; at least this is true from clinical observations, for there are few reports of either surgical or morbid anatomy of lymphosarcomatous invasion of the nervous system and its envelopes.

It has been emphasized frequently that the symptoms in this group are produced commonly by tumors attacking the posterior cervical chain of lymphatics, causing extracranial lesions, although this rarely may be due to their local intracranial extension. These lesions give rise to irritative or paralytic symptoms from the last four cranial nerves and the cervical sympathetic nerves, thus producing the several well known syndromes (the syndromes of the posterior lacerated foramen or jugular foramen [Vernet [20]]; condylojugular foramens [Collet [21] and Sicard [22]];

15. Sugarbaker, E. D., and Craver, L. F.: Lymphosarcoma: A Study of One Hundred and Ninety-Six Cases with Biopsy, J. A. M. A. **115**:17-23 (July 6) 1940.

16. Tonsils, 14 per cent; nasopharynx, 5 per cent; parotid gland, 1 per cent; antrum, 1 per cent; orbit, 0.5 per cent; eyelids, 0.5 per cent (based on the entire group [196 cases]).

17. In a survey of the clinical and pathologic problems in this connection C. Davison and J. J. Michaels (Lymphosarcoma with Involvement of the Central Nervous System, Arch. Int. Med. **45**:908-925 [June] 1930) reported 7 cases in which there were neurologic symptoms out of 26 cases of lymphosarcoma, in all of which the growths clinically belonged in the first group, subsequently described in the text.

18. Woltman, H. W.: Malignant Tumors of the Nasopharynx with Involvement of the Nervous System, Arch. Neurol. & Psychiat. **8**:412-429 (Oct.) 1922.

19. Bassoe [3] reported a case in 1922, the year in which Woltman's paper appeared. In Bassoe's case the clinical diagnosis (from a cervical biopsy) was Hodgkin's disease, but at necropsy there was an infiltration of the cerebral dura mater with formation of nodules. Histologically, the disease was proved to be lymphosarcoma. As to the situation of Hodgkin's disease, the literature is replete with reports of invasion of the intracranial and intraspinal dura mater. This is shown in the recent summary of the literature by K. O. Von Hagen (Lymphogranuloma [Hodgkin's Disease] with Involvement of the Spinal Cord, Bull. Los Angeles Neurol. Soc. **2**:20-25 [March] 1937.

20. Vernet, M.: Sur le syndrome des quatre dernières paires crâniennes, d'après une observation personnelle chez un blessé de guerre, Bull. et mém. Soc. méd. d. hôp. de Paris **40**:210-223, 1916.

(Footnotes continued on next page)

posterior retroparotid space [Villaret [23]], and dissociated forms of the posterior syndrome as reported by Avellis [24] [tenth nerve], Schmidt [25] [eleventh nerve], Jackson [26] [tenth, eleventh and twelfth nerves] and Tapia [27] [tenth and twelfth nerves]). Other cranial nerves may also be attacked and give rise to symptoms of irritative or paralytic nature, but such lesions occur less frequently than those affecting the last four cranial nerves and they are more common in the second group than in the first.

As to the second group, the French and Italian neurologists and otolaryngologists have shown a great interest in this problem and have directed attention to tumors whose origin is "peritubal" (eustachian). Jacod has stressed that intracranial extension of such tumors invariably occurs and produces neurologic symptoms because the fascial anatomic relations of this region with the base of the skull are different from those of any other region, allowing spread of the neoplasm upward to the petrosphenoidal (anterior lacerated) space, which gives access to structures in the middle fossa. The syndrome most commonly encountered is produced by irritation or paralysis of one or all branches of the trigeminal nerve and the oculomotor nerve; however, the complete syndrome is characterized by involvement of all the cranial nerves in the middle fossa (*syndrome du carrefour pétrosphenoïdal* second, third, fourth, fifth and sixth cranial nerves).[28] Similar observations have been described by many others; however, it has also been demonstrated that on rare occasions a tumor arising elsewhere (other than "peritubal" or in the "cavum") may spread or metastasize into this region and produce the same syndrome as well as involve other of the cranial nerves, giving rise to motor and sensory ophthalmoplegia and to paralysis of other cranial nerves (sixth, seventh [uncommonly involved], ninth, tenth, eleventh and twelfth). This, however, is probably rare. Other symptoms are frequently due to increased intracranial pressure caused by the presence of the rapidly growing mass, and occa-

21. Collet, M.: Sur un nouveau syndrome paralytique pharyngo-laryngé par blessure de guerre (Hémiplégié glosso-laryngo-scapulo-pharyngée), Lyon méd. **124**:121-129, 1915.

22. Sicard, J. A.: Syndrome du carrefour condylo-déchiré pòstérieur (type pur de paralysie des quatre derniers nerfs craniens), Bull. et mém. Soc. méd. d. hôp. de Paris **41**:317-327, 1917.

23. Villaret, cited by Wilson, S. A. K., and Bruce, A. N.: Neurology, Baltimore, William Wood & Company, 1940, vol. 1, p. 426.

24. Avellis, G.: Klinische Beiträge zur halbseitigen Kehlkopflähmung, Berl. Klin. **40**: 1-26, 1891.

25. Schmidt, cited by Wilson, S. A. K., and Bruce, A. N.: Neurology, Baltimore, William Wood & Company, 1940, vol. 1, p. 426.

26. Jackson, J. H.: Paralysis of Tongue, Palate, and Vocal Cord: Treatment of Obscure Forms of Metrorrhagia, Lancet **1**:689-690 (April 10) 1886.

27. Tapia: Un nouveau syndrome: quelques cas d'hémiplégie du larynx et de la langue avec ou sans paralysie du sterno-cléïdo-mastoïdien et du trapèze, Arch. internat. de laryng. **22**:780-785, 1906.

28. M. Jacod (La sindrome di Silvio Negri: A propos des cancers péritubaires et de leur propagation endocranienne, Riv. oto-neuro-oftal. **12**:523-529 [July-Aug.] 1935) has reproduced an obscure article written and published in 1888 in Turin, Italy, by Silvio Negri, who apparently was the first to describe the syndrome of this region and substantiate the pathology of it (Negri, S.: La sindrome di Silvio Negri. Storia d'un tumore della base del cranio. Cenni sulla malattia del Comm. Mons. Bernardo Raineri. Reperto necroscopico, ibid. **12**:515-522 [July-Aug.] 1935). In Italian and French literature the syndrome has recently been described under the name of "Negri-Jacob Syndrome." This is to be differentiated from the syndrome of Gradenigo or "syndrome of the petrous apex," which involves only the fifth and sixth cranial nerves (Gradenigo, G.: Ueber die Paralyse des Nervus abducens bei Otitis, Arch. f. Ohrenh. **74**:149-187, 1907).

sionally there is evidence of infiltration of the brain itself, though this is rarely suspected until proved at necropsy or by surgical exploration and it appears to be rather infrequent, if not rare.[29]

From the pathologicoanatomic standpoint, the process consists of an infiltration of the dura mater until its structure is no longer grossly recognizable and of subsequent formation of tumor nodules. Or the lesion may appear as a friable, flat subdural mass of a few millimeters' thickness, not unlike an organizing subdural hematoma, which can be stripped easily from the inner surface of the dura mater.[30] Occasionally there is extension of the morbid process into the arachnoid and subarachnoid space and, finally, perivascular extension into the cortex of the brain.[31] Cranial nerves are involved in the neoplastic processes both by compression and by infiltration, with concomitant interference with their function.

The third group mentioned previously, the tumors in which the spinal cord is involved, is better known than the first and second groups and is one in which the literature is much more voluminous. Because of its individual nature and problems peculiar to it, it would not be possible or expedient to discuss the group here. Suffice it to say that the spinal dura mater is involved frequently and the cord is damaged in one of the following ways or by a combination of them: (1) compression by the presence of the space-occupying new growth, (2) interference with its vascular supply and lymphatic drainage, or (3) direct extension into it by the neoplasm. Interestingly, there are problems which are special to different regions of the spinal column.

Much has been said about intracranial extension of lymphosarcoma, but we have here presented 2 cases in which the primary lesion appears to have been within the cranial dura mater. These are undoubtedly unique, for we have been unable to find a similar report anywhere in the literature. Therefore, the question whether the tumors reported on here were primary within the cranial bones or within the dura mater is important, but it appears to be fairly well answered in case 1 by the thorough necropsy. In case 2 in which there was a lamented lack

29. It is recognized that metastatic tumors (lymphosarcoma) may invade the brain more frequently than previously had been anticipated or even disseminate through it and its cavities, since altogether too frequently the author reporting such a growth has merely stated that there was "involvement of the brain" or "involvement of the nervous system." In a recent article (Gross, P., and Votawa, G. J.: Bilateral Symmetrical Exophthalmos Due to Retrobulbar Lymphosarcoma: Report of a Case, Radiology **31**:620-621 [Nov.] 1938) the authors dismissed the intracranial findings with the statement that the choroid plexus was the site of metastatic nodules; this is undoubtedly of uncommon occurrence, though we have several such examples of metastatic lesions in the Mayo Clinic series.

30. This was the situation in the case of a woman aged 46 years, whom we have recently had the privilege of studying. Because of a history of multiple infections in the past seven years, including an abscess in the left frontotemporal region of the scalp, her present symptoms of fever, leukocytosis and sudden onset of aphasia, delirium and right hemiparesis were interpreted as caused by an infection. A subsequent drop of both temperature and number of leukocytes with a rather rapid onset of coma was taken to indicate encapsulation of an abscess of the brain in the left frontotemporal region. A small craniotomy was therefore performed, but to our surprise we encountered a subdural mass of friable tissue about 8 by 10 cm. and 3 to 6 mm. thick. Since sufficient time has not elapsed for thorough study, we submit this brief résumé as only a possible case of primary intracranial lymphosarcoma. It clinically conforms to this group and in all probability will prove to be one.

31. In surveying the literature of Hodgkin's disease it was apparent that either the invasion of the nerve tissue secondary to its invasion of the dura mater was more common than that of lymphosarcoma or there has been a greater interest over a longer period in Hodgkin's disease than in lymphosarcoma. Possibly both factors play a role.

of study at necropsy, the question seems well answered by careful analysis of the clinical records and by the fact that so far lymphosarcoma has not been reported as primary in the skull.[32]

It may be well to enumerate those incidents in this case which lend credence to the primary intracranial origin of the lesion. They are as follows: 1. The primary symptoms were signs of increased intracranial pressure (headache, vertigo, tinnitus, malaise, anorexia, diminished vision, motor weakness and numbness and paresthesias of the finger tips). 2. The lump in the frontoparietal region of the scalp appeared after the first signs of involvement of the nerve tissue were manifested. 3. There was no evidence of cervical adenopathy or enlargement or infiltration of any of the structures at the base of the skull. 4. The neoplasm was found by surgical intervention. 5. The involvement of cerevical lymph nodes appeared after surgical interference with the local mass, allowing spread of the lymphosarcoma through the tissues of the scalp into the cervical nodes. 6. The disease had a long course. 7. There was no evidence of tumor elsewhere in the body. 8. The tumor was present in the vault and not in the base of the skull, where tumors of "peritubal" or of cervical lymph node origin are prone to make themselves apparent. In the first statement in the foregoing list, it is well to note that in other cases in which there were intracranial metastatic growths the first symptoms have been cervical adenopathy or primary extranodal symptoms and subsequent compression of certain cranial nerves making exit through the basilar foramens, whereas this patient's symptoms, as previously pointed out, were first of all indicative of their intracranial origin.

From the point of view of pathology one may justifiably question the dural origin of the lesion in favor of its arising primarily in the diploe of the overlying skull. Since the first patient had received a seemingly minor injury to the skull, as we have mentioned already, it is conceivable that this may have produced enough reaction to form a focus of lymphocytes in the dura mater in which the tumor could have originated later. But in the second case there was no history of trauma; although the largest portion of the tumor was in the dura mater and infiltrated the adjacent leptomeninges and brain, certainly its dural origin cannot be postulated or established so easily. The absence of lymphatics within the dura mater and the leptomeninges, now well known because of the work of Weed[33] in

32. L. F. Graver and M. M. Copeland (Lymphosarcoma in Bone, Arch. Surg. **28**:809-824 [May] 1934) indicated the skull as the third most common site of metastatic lymphosarcoma but did not report any such tumor as primary in the cranial bones. More recently, Parker and Jackson[12] have established primary reticulum cell sarcoma of bone as a distinct clinical entity, though it is histologically identical with the same tumor of the soft parts, but they did not find any such growth primary in the cranial bones. Szutu and Hsieh, who have recently reported on this tumor (Szutu, C., and Hsieh, C. K.: Primary Reticulum Cell Sarcoma of Bone: Report of 2 Cases with Bone Regeneration Following Roentgenotherapy, Ann. Surg. **115**:280-291 [Feb.] 1942), did not mention it as occurring in the skull nor have we been successful in locating any such report in any of the literature available to us as late as January 1943.

33. Weed, L. H.: Studies on Cerebro-Spinal Fluid: II. The Theories of Drainage of Cerebro-Spinal Fluid with an Analysis of the Methods of Investigation, J. M. Research **26**: 21-49 (Sept.) 1914; III. The Pathways of Escape from the Subarachnoid Spaces with Particular Reference to the Arachnoid Villi, ibid. **26**:51-91 (Sept.) 1914; IV. The Dual Source of Cerebro-Spinal Fluid, ibid. 93-117 (Sept.) 1914. Weed, L. H.: The Meninges, with Special Reference to the Cell Coverings of the Leptomeninges, in Penfield, W.: Cytology and Cellular Pathology of the Nervous System, New York, Paul B. Hoeber, Inc., 1932, vol. 2, pp. 613-634.

1914, is also against either tumor's having its origin in this structure.[34] However, little work has been done on the late effects (the presence of residual lymphoid elements) of trauma and infection[35] in the dura; consequently the dura mater remains as a possible site of origin for such a neoplastic process.

Although these cases suggest such an origin they fall far short of proving it. Hence the primary development of such tumors may more probably be in the diploe of the skull. With this in mind, a search through the records of tumors of the skull studied at the clinic was made in the hope of finding a record of a lymphosarcoma localized to this structure without metastasis or extension into the surrounding tissue. This yielded a record of a case in which operation was performed and in which there were bilateral parietal subperiosteal tumors with roentgenographic evidence of multiple areas of erosion of the skull, not unlike the changes seen secondary to an underlying meningioma (roentgenographic diagnosis). However, this patient was without clinical evidence of intracranial extension. The subperiosteal tumors were removed surgically, and the underlying eroded bone was cauterized extensively with the electrosurgical unit. The operative site and surrounding areas were subsequently exposed to roentgen therapy. It is known that for seven years there was no recurrence of the neoplasms or evidence of metastasis. The tissue appeared to be a lymphosarcoma, and review of the slides confirmed this interpretation, for it was composed of lymphocyte-like cells and others resembling reticulum cells. In fact, the latter cells tended to predominate; consequently this is probably a lymphosarcoma of the reticulum cell type or possibly of a mixed type as described by Warren and Picena.[36]

That lymphosarcoma can and does arise in bone has been known for several years, and this case might suggest just such an origin in the cranial bones for the

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34. H. Rouvière (Anatomy of the Human Lymphatic System, translated by M. J. Tobias, Ann Arbor, Mich., Edwards Brothers, Inc., 1938, pp. 238-239) expressed the opinion that lymph crevices exist in the dura mater and communicate with adjacent channels and nodes, though he failed to state where these are or what is the nature of the "lymph crevices." Moreover, he did not state his authority for these statements, not even his own investigations. However, in substantiating his statement on the presence of pial perivascular lymph vessels he quoted the obsolete reports of the last century and before, such as those of Mascagni in 1787 and Fohman in 1838. C. K. Drinker and J. M. Yoffey (Lymphatics, Lymph, and Lymphoid Tissues, Cambridge, Mass., Harvard University Press, 1941, p. 7) in 1941 noted the presence of lymphatics leading from the cranium but did not mention any afferents to these. Possibly these as well as the basilar foramens are channels for the extension into the intracranial structures from cervical lymphosarcoma, as has been noted by C. Jemmi (Su di un interessante caso di linfosarcoma peritubarico con diffusione intracranica. Riv. oto-neuro-oftal. **15**:336-348 [July-Aug.] 1938), L. de Lisi (Complicazioni nervose del linfosarcoma: necrosi midollare acuta; invasione endocranica bilaterale, sindrome della fossa petro-sfenoidale, Riv. oto-neuro-oftal. **12**:209-238 [March-April] 1935), H. R. Viets and F. T. Hunter (Lymphoblastomatous Involvement of the Nervous System, Arch. Neurol. & Psychiat. **29**:1246-1261 [June] 1933), D. Paulian, I. Bistriceanu and M. Cardas (Sarcome lymphoblastique médiastinal avec métastases ganglionnaires et encéphalo-craniennes, Arch. de neurol. **3**:268-274, 1929), Woltman[18] and Davison and Michaels,[17] among others.

35. In this connection it is of interest to surmise the possible role of infection as a predisposing cause of lymphosarcoma. In our first case the patient did have a small active lesion of pulmonary tuberculosis which would have been difficult to diagnose clinically, but there was no evidence of tuberculosis elsewhere in the body. In another case (footnote 30) the patient whom we have recently studied had had many infections, one of which was an abscess in the left frontotemporal region of the scalp. Lymphosarcoma later developed immediately beneath this area in the dura mater. Just what relation exists between these lesions may be difficult to prove, but it does seem possible that the one predisposed to the other.

36. Warren, S., and Picena, J. P.: Reticulum Cell Sarcoma of Lymph Nodes, Am. J. Path. **17**:385-393 (May) 1941.

lesions in the 2 cases we have reported herein. But wherever the origin may have been, these interesting cases emphasize our ignorance of this group of tumors and the need for investigation of their possible origin in nonlymphatic structures as well as in the cranial bones.

SUMMARY

We have described what appear to have been 2 primary lymphosarcomas of the intracranial dura mater, the one occurring in a man and the other in a woman, aged 24 and 57 years, respectively. A third case, mentioned briefly, is possibly an instance of this type of tumor, but to date we have only surgical confirmation of the growth's belonging to this group.

The problems of the origin of these tumors either in the dura mater over the dorsolateral surface of the brain or in its contiguous overlying cranial bone have been discussed. It was admitted that the latter as the primary site of origin could not be ruled out; the tumors may well have arisen in the bony diploe of the skull.

The usual sites of origin of lymphosarcoma in the head (extracranial) have been reviewed, including the various modes of intracranial extension and the several syndromes thereby provoked (Jacod-Negri syndrome, syndromes of the last four cranial nerves, of the superior cervical sympathetic nerves, and so forth). These were contrasted with the symptoms described in 2 cases reported here.

Mayo Clinic.

EFFECT OF DIVISION OF THE SPHINCTER OF ODDI ON THE BILE DIASTASE OF THE DOG

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The observations of Opie [1] and others have established that in about 25 per cent of normal persons the ends of the common bile and main pancreatic ducts join at or before the papilla of Vater, resulting in a confluence of the secretions of these two ducts, the "common channel." Thus the anatomic arrangement is such that a calculus at the outlet, a spasm of the sphincter of Oddi or edema of the duodenal mucosa may cause reflux of the secretion from one into the other duct. That reflux of bile into the pancreatic duct may be an important factor in the causation of acute pancreatitis in some cases seems well established.

More recently considerable evidence has accumulated to indicate that the flow may be reversed, i. e., that there can be a reflux of pancreatic juice into the biliary tract.[2] The strongest evidence that this occurs has been based on the appearance of diastase in the bile of patients whose common bile ducts have been drained.[3] Normally, hepatic bile is almost devoid of diastase.[4] Bile from the gallbladder likewise contains no diastase or only minute amounts, considerably less than that contained in the blood.[5] The appearance of appreciable amounts of diastase in the bile of patients who have undergone surgical operations [6] indicates that pan-

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1. Opie, E. L.: Diseases of the Pancreas, ed. 2, Philadelphia, J. B. Lippincott Company, 1910.

2. (*a*) Bundschuh, E.: Gleichzeitige Bauchspeichel- und Gallenperitonitis zugleich ein Beitrag zur Kenntnis der Ätiologie der perforationslosen Gallenperitonitis, Deutsche Ztschr. f. Chir. **203-204**:233, 1927. (*b*) Westphal, K.: Die durch Dyskinese der Ausführungsgänge bedingten Pankreasfermentschädigungen an den Gallenwegen und der Leber, Ztschr. f. klin. Med. **109**:55, 1929. (*c*) Wolfer, J. A.: The Role of the Pancreatic Juice in the Production of Gall Bladder Disease, Surg., Gynec. & Obst. **53**:433, 1931. (*d*) Popper, H. L.: Pankreassaft in den Gallenwegen. Seine pathogenetische Bedeutung für die Entstehung der akuten Pankreaserkrankungen, Arch. f. klin. Chir. **175**:660, 1933. (*e*) Colp, R.; Gerber, I., and Doubilet, H.: Acute Cholecystitis Associated with Pancreatic Reflux, Ann. Surg. **103**:67, 1936. (*f*) Wolfer, J. A.: Pancreatic Juice as a Factor in Etiology of Gall Bladder Disease, Surgery **1**:928, 1937. (*g*) Colp, R., and Doubilet, H.: The Operative Incidence of Pancreatic Reflux in Cholelithiasis, ibid. **4**:837, 1938; (*h*) The Clinical Significance of Pancreatic Reflux, Ann. Surg. **108**:243, 1938.

3. (*a*) Probstein, J. G.; Heifetz, C. J., and Gray, S. H.: Diastase in Human Bile, to be published. (*b*) Colp and Doubilet.[2g, h]

4. (*a*) Gray, S. H.; Probstein, J. G., and Heifetz, C. J.: Clinical Studies on Blood Diastase: I. Low Blood Diastase as an Index of Impaired Hepatic Function, Arch. Int. Med. **67**:805 (April) 1941. (*b*) Popper.[2d]

5. Colp and Doubilet.[2g] Gray, Probstein and Heifetz.[4a]

6. Popper.[2d] Colp and Doubilet.[2g]

creatic juice has in some manner entered the biliary tract. In the human being the common channel has been held responsible for this occurrence, and the confluence has been proved roentgenologically.[2h] It is not possible to state at this time whether regurgitation of duodenal contents (containing pancreatic juice) through a relaxed sphincter of Oddi can or does occur. But the following experiments seem to indicate that division of the sphincter of Oddi in dogs will permit regurgitation of duodenal contents into the biliary tree. The existence of a common channel in the dog has never been demonstrated.

METHODS

Normal, apparently healthy dogs were employed in two series of experiments. In the first, 3 dogs were used to ascertain normal bile diastase values. The animals were anesthetized with pentobarbital sodium, 0.5 cc. of a 6.7 per cent solution being given intravenously for each kilogram of body weight.[7] The abdomen was entered through a high midline incision, and the gallbladder and bile ducts exposed with as little trauma to the surrounding structures as possible. A fine aspirating needle was inserted through an avascular area in the wall of the fundus and 5 to 10 cc. of bile was removed. The common bile duct was exposed close to the junction with the duodenum and divided between clamps, and each end was ligated with silk. A small intercostal incision on the right side was then made between the two lowermost ribs, overlying the fundus of the gallbladder. It was sometimes necessary partly to free the gallbladder from the bed of the liver to effect delivery of the gallbladder through this incision. The wall was sutured to the edges of the skin with fine interrupted silk sutures, the portion of the organ previously used for aspiration being allowed to protrude about 1 cm. above the skin. A purse-string silk suture was then applied around the protruding serosa, a flanged straight metal cannula with an opening 4 mm. in diameter introduced through an appropriate-sized incision and the purse-string closed, so as to invert the edges of the incision in the gallbladder. Sometimes it was necessary to apply a second inverting purse-string suture. The length of the cannula depended on the thickness of the walls of the abdomen and the gallbladder and on its direction through these layers, but the average length was 4 cm., about 8 mm. of which was permitted to protrude beyond the skin. The cannula was flushed out with saline solution to remove blood clots, and the abdominal wall was closed in layers snugly around the cannula. By this method a steady flow of hepatic bile was secured, and the possibility of regurgitation from the pancreatic duct or the duodenum was precluded. Specimens consisting of 4 to 6 cc. of bile were collected daily for determinations of diastase, the remainder being discarded.

The common ducts of the dogs in the second series were not severed. Instead, the opening of the common bile duct into the duodenum was exposed transduodenally. This opening could usually be located without difficulty on a small mucosal papilla. When probed the duct was found to traverse the duodenal wall at an acute angle with the long axial plane of the mucosa, forming between the two lumens a musculomucosal flap which contained fibers of the sphincter of Oddi. With one blade of a thin scissors inserted in the common bile duct and the other placed on the duodenal mucosa, this flap was cut for a distance of nearly 1 cm. A wide channel between the duodenum and the common bile duct was thereby created. The duodenum was then flushed out with saline solution and closed with two layers of fine intestinal sutures. The gallbladder was cannulized in the manner described, and the external opening of the cannula stoppered. By removal of the stopper specimens consisting of 3 to 6 cc. of bile were collected by gravity flow. It was found that the bile could be collected faster after the animals were fed. The otherwise normal flow of bile into the intestine permitted the maintenance of adequate nutrition.

Several dogs subjected to this procedure were killed at the conclusion of the experiment and examined for patency of the choledochoduodenal communication. In all cases the operative wound had healed well and the opening was practically as wide as when first made.

After perfection of the technic it was possible to collect bile samples minimally contaminated by blood or by tissue juices. The appearance of blood in a bile sample necessitated its rejection, for the blood of a dog contains large amounts of diastase (about ten times that contained in human blood).

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7. All types of anesthesia except that induced with chloroform exert no effect on blood diastase values and hence probably do not affect the amount of diastase in the bile (Probstein, Heifetz and Gray [3a]).

Determinations of diastase were performed by the Somogyi technic for diastase activity of the blood [8] modified by him for determinations of diastase activity of the bile as follows:

1. The bile is neutralized to phenolsulfonphthalein by addition of some powdered buffer mixture with a p_H of 7.[9]

2. Five cubic centimeters of the starch paste [8] and 1 cc. of a 1 per cent solution of sodium chloride are mixed in a test tube. The mixture is placed in a water bath at 40 C. for a few minutes and allowed to reach that temperature.

3. One cubic centimeter of the neutralized bile is added, and the mixture is incubated at 40 C. for thirty minutes.

4. One cubic centimeter of 5 per cent zinc sulfate solution is added to the mixture, and after agitation 1 cc. of 0.3 normal barium hydroxide solution [10] is added to precipitate the proteins. The contents are mixed and centrifuged for about five minutes. This step is to be performed without delay, because precipitation does not completely stop the diastatic activity.

5. After centrifugation the supernatant fluid is filtered, and a drop of phenolsulfonphthalein solution is added to the filtrate. Crystals of powdered sodium carbonate are then added until the indicator shows an alkaline reaction.

6. If the liquid appears turbid, it is centrifuged and filtered again.

7. The sugar is determined in this filtrate with the high alkalinity copper reagent.[11] Five cubic centimeters of the filtrate and 5 cc. of the reagent are used, and the mixture is heated in a water bath for twenty minutes.

8. To determine the original reducing power of the bile 1 cc. of bile is added to 6 cc. of water and precipitated with 2 cc. of 5 per cent zinc sulfate solution and 1 cc. of 0.3 normal barium hydroxide solution. From then on the mixture is treated as the bile–starch–saline solution mixture.

9. The reducing power of the bile in terms of dextrose expressed in milligrams per hundred cubic centimeters is subtracted from the value obtained for the sugar content of the incubated bile–starch–saline solution mixture.

10. If the values for diastase activity are exceedingly high, as often happens when one is working with dogs, the determination should be repeated with bile diluted 1:5 or 1:10 with water.

RESULTS

The values for diastase activity of the bile obtained from the 3 control dogs are compiled in table 1. The almost negligible amounts of diastase present are comparable to those in human beings. Measurable amounts were found for the first two or three days after the operation, which perhaps indicates admixture with minute amounts of blood or tissue juices. The results of tests on bile specimens taken from dog 2 before and after feeding indicate that ingestion of food has no effect on the diastase values, a result similar to the lack of effect of food on animal and human blood diastase.[12]

Table 2 shows the values for diastase activity of the bile of the dogs subjected to division of the sphincter of Oddi. In 5 dogs (4, 6, 11, 13 and 16) technical mishaps or death of the animal prevented obtaining bile samples after the initial gallbladder aspiration samples were secured. In the remaining dogs from the first postoperative day there was a great increase in the diastase content of the

8. Somogyi, M.: Micromethods for the Estimation of Diastase, J. Biol. Chem. **125**:399, 1938.

9. Hunt, G. A.: Dry Buffer Salt Mixtures for Use in Biological Preparations, J. Lab. & Clin. Med. **28**:97, 1942.

10. Weichselbaum, T. E., and Somogyi, M.: A Method for the Determination of Small Amounts of Ketone Bodies, J. Biol. Chem. **140**:12, 1941.

11. Somogyi, M.: Detection and Quantitative Determination of Small Amounts of Glucose in Mixtures Containing Maltose, J. Biol. Chem. **119**:741, 1937.

12. Somogyi, M.: Diastatic Activity of Human Blood, Arch. Int. Med. **67**:665 (March) 1941.

TABLE 1.—*Values for Diastase Activity in Cannulated Bile from the Gallbladder of Dogs Whose Common Bile Duct Was Divided*

Postoperative Day	Dog 1, Before Feeding	Dog 2		Dog 3, Before Feeding	Average Before Feeding
		Before Feeding	After Feeding		
0	0	0	..	0	0
1	23	140	109	34	66
2	10	32	40	18	20
3	0	0	20	0	0
4	0	0	0	0	0
5	..	40	30	0	20
6	..	40	0	..	40
7	0	..	..	..	0
8	..	..	..	0	0
9	123	..	..	..	123
10	..	..	..	0	0
11	0	0	0	..	..
12	..	..	..	..	..
13	..	..	..	0	0
14	..	..	..	..	..
15	0	..	..	..	0
16	0	0	0	..	0
17	..	..	..	0	0
18	..	..	..	..	..
19	..	0	..	..	0
20	..	..	..	0	0
21	..	0	..	..	0

TABLE 2.—*Values for Diastase Activity in Cannulated Bile from the Gallbladder of Dogs Whose Sphincter of Oddi Was Divided*

Postoperative Day	Dog 4	Dog 5	Dog 6	Dog 7	Dog 8	Dog 9	Dog 10	Dog 11	Dog 12	Dog 13	Dog 14	Dog 15	Dog 16
0	0	0	0	102	0	0	0	35	0	0	235	0	0
1	..	803	..	536	...	138	922	..	423	..	...	803	..
2	..	..	..	623	238	298	1,014	..	379	..	1,800	...	..
3	..	..	..	...	1,011	932	653	..	690	..	...	155	..
4	..	..	..	1,032	932	...	1,081	..	...	..	...	140	..
5	..	..	..	...	808	710	749	..	...	..	...	725	..
6	..	..	..	...	383	608	...	..	430	..	...	...	..
7	..	..	..	...	444	543	...	..	...	..	...	520	..
8	..	..	..	...	0	...	251	..	...	..	...	740	..
9	..	..	..	...	202	724	...	..	330	..	...	180	..
10	..	..	..	...	...	...	597	..	860	..	...	830	..
11	..	..	..	...	304	730	656	..	945	..	...	930	..
12	..	..	..	...	308	...	880	..	143	..	...	...	..
13	..	..	..	...	...	1,423	...	..	756	..	...	803	..
14	..	..	..	...	423	808	0	..	238	..	...	...	..
15	..	..	..	...	...	...	655	..	...	..	...	1,235	..
16	..	..	..	...	...	623	645	..	683	..	...	...	..
17	..	..	..	...	...	436	...	..	...	..	...	1,460	..
18	..	..	..	...	932	...	...	..	...	..	...	...	..
19	..	..	..	...	...	...	475	..	943	..	...	...	..
20	..	..	..	...	108	84	...	..	1,032	..	...	830	..
21	..	..	..	475	...	510	520	..	...	..	...	...	..
22	..	..	..	...	446	562	485	..	...	..	...	...	..
23	..	..	..	...	...	...	490	..	...	..	...	554	..
24	..	..	..	...	248	...	240	..	...	..	...	...	..
25	..	..	..	...	243	...	740	..	...	..	...	...	..
26	..	..	..	...	...	...	...	..	...	..	...	220	..
27	..	..	..	...	...	...	...	..	...	..	...	...	..
28	..	..	..	...	0	...	666	..	...	..	...	...	..
29	..	..	..	...	...	...	589	..	...	..	...	635	..
30	..	..	..	...	...	...	1,380	..	...	..	...	...	..
31	..	..	..	...	...	...	...	..	...	..	...	...	..
32	..	..	..	...	...	...	554	..	...	..	...	435	..
33	..	..	..	...	...	...	...	..	...	..	...	...	..
34	..	..	..	...	...	...	...	..	...	..	...	...	..
35	..	..	..	...	...	...	220	..	...	..	...	...	..
36	..	..	..	...	...	...	1,290	..	...	..	...	...	..
37	..	..	..	...	...	...	...	..	...	..	...	...	..
38	..	..	..	...	...	...	...	..	...	..	...	...	..
39	..	..	..	...	...	...	795	..	...	..	...	...	..

cannulated bile. This increase was maintained with few exceptions at a relatively constant level for a period as long as the experiments lasted, up to thirty-eight days. The sudden disappearance of diastase from the bile in an occasional sample is somewhat difficult to explain. It is likely that a temporary blockage to the reflux of duodenal contents may have resulted from a plug of mucus or a particle of solid food. A notable and not anticipated observation was that there was so little variability in the diastase content from day to day.

COMMENT

It can be concluded from these experiments that normally the hepatic or gallbladder bile of the dog contains no diastase or negligible amounts of it. It is also evident that when the sphincter of Oddi is divided, assuming *a priori* that the diastase comes from the duodenal juice, there is a reflux of duodenal contents into the biliary tree. Furthermore, at least when the cannula is inserted, some of the contents rise as high as the gallbladder. Whether the contents would reach this level had not the gallbladder been decompressed by the insertion of the cannula cannot be answered from these experiments. Furthermore, it has not been proved that a similar reflux can occur without division of the sphincter of Oddi. Such experiments, however, are quite feasible. Our experiments likewise throw little light on the occurrence of this reflux in the human being; nor has the opportunity to perform the needed experiments for verifying this assumption presented itself. That spasm of the sphincter of Oddi does occur has been adequately demonstrated. It is almost axiomatic that if muscular spasm occurs, its opposite, muscular relaxation, must also sometimes be present. Whether this relaxation is sufficient to permit reflux of duodenal contents into the biliary tract is yet unanswered. If it does occur, a potential etiologic factor of disease of the biliary tract is apparent.

It has been suggested that in some cases acute cholecystitis may have as an etiologic factor the reflux of pancreatic juice into the gallbladder.[13] This evidence also rests largely on the finding at operation of appreciable amounts of diastase in bile from the gallbladder of these patients. Unfortunately any effect of the prolonged reflux of duodenal contents into the gallbladders of our dogs might be obscured by the irritative effects of the cannula. It was noted at autopsy, for instance, that the gallbladders of these animals were thickened and scarred and so contracted as to envelop the cannula closely. It could hardly be concluded from this that the reflux of bile was totally responsible for the pathologic change.

CONCLUSION

When the sphincter of Oddi is divided and a cannula inserted into the gallbladder of the dog, there results a reflux of duodenal contents into the common bile duct and gallbladder as measured by the appearance of diastase in the cannulated bile.

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UNUSUAL CASES OF HYPERINSULINISM AND HYPOGLYCEMIA

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SAN FRANCISCO

I. EXTRAPANCREATIC ISLET ADENOMA AS A CAUSE OF HYPERINSULINISM AND HYPOGLYCEMIA

Masses of aberrant pancreatic tissue varying greatly in size have been described by many authors since Klob's[1] first report in 1859. Faust and Mudgett[2] in 1940 recorded the locations of such aberrant tissue in 370 published cases (table) as follows:

	No. of Cases		No. of Cases
Stomach	95	Diverticulum (not located)	1
Duodenum	105	Umbilical fistula	1
Duodenojejunal angle	2	Mesentery	3
Jejunum	65	Omentum	4
Ileum	18	Splenic capsule	3
Small intestine	6	Spleen	1
Diverticulum of stomach	3	Gallbladder	3
Diverticulum of duodenum	7	Cystic duct	1
Diverticulum of jejunum	1	Gastrocolic ligament	1
Diverticulum of ileum	8	Transverse mesocolon	1
Diverticulum of small intestine	2	Location questionable	18
Meckel's diverticulum	21		
			370

Exceedingly variable symptoms are attributable to aberrant pancreatic tissue. These symptoms may be indistinguishable from those due to simple ulcer, such as anorexia, nausea, vomiting, epigastric pain, insomnia and loss of weight. Symptoms not unlike those due to appendicitis, cholecystitis or diverticulitis have been described in association with or directly attributable to this extrapancreatic tissue. Symptoms of obstruction due to intussusception have been precipitated by abnormally placed pancreatic tissue within the lumen of the bowel. Insidiously progressive digestive disturbances together with debility and loss of weight have suggested the presence of cancer of some intra-abdominal organ.

In the reports of the cases recorded in the tabulation no mention is made of the symptoms of hyperinsulinism associated with aberrant pancreatic tissue. However, in October 1941 Rudd and Walton[3] reported the case of a young man, of 29, with an extrapancreatic islet adenoma half an inch (1.3 cm.) in diameter located in the "lower part of the gastrosplenic omentum, about 1 inch (2.5 cm.) beyond

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1. Klob, J.: Pancreas-Anomalien, Ztschr. d. k. k. Gesellsch. d. Aerzte zu Wien **15**: 732, 1859.

2. Faust, D. B., and Mudgett, C. S.: Aberrant Pancreas, with Review of Literature and Report of a Case, Ann. Int. Med. **14**:717-728 (Oct.) 1940.

3. Rudd, T. N., and Walton, J.: A Case of Islet Adenoma of the Pancreas, Brit. J. Surg. **29**:266-270 (Oct.) 1941.

the lower part of the tail of the pancreas," which had been responsible for such pronounced symptoms of hyperinsulinism as epileptiform attacks, deep stupor, unconsciousness, Cheyne-Stokes respiration, drenching sweat, incontinence and rigidity of limbs, all relieved by intravenous administration of dextrose. Also experienced by this patient were morning stupor, mental confusion and loss of memory, which were relieved by a cup of sweetened tea. Slowness of speech, dulness of mentality, general weakness and muscular tremors, suggesting a parkinsonian syndrome, had also been noted. Values for blood sugar as low as 48 and 40 mg. per hundred cubic centimeters were recorded before operation. All these varied symptoms were completely relieved by the removal of the small extrapancreatic islet tumor lying in the gastrosplenic mesentery.

In February 1942 Smith [4] reported the case of a woman 45 years of age with a long history of a variety of complaints, including sinus infection, "dropped stomach," sick headaches, cystitis, nervousness, emotional instability, menorrhagia, anemia and pronounced general weakness and faintness relieved only by the frequent administration of food—as many as eleven meals in twenty-four hours. On one occasion a blood sugar concentration of 37 mg. per hundred cubic centimeters was recorded, associated with extreme weakness, profuse sweating and trembling, which could be relieved by eating a slice of toast. At operation for a presumed islet tumor, the pancreas was found to be normal, but on the descending portion of the duodenum just below the superior duodenal flexure there was a nodule of tissue approximately 2 by 1.5 by 0.5 cm., weighing 1.5 Gm., which microscopic examination revealed to be pancreatic tissue consisting of acini and ducts, with a few well circumscribed islets and numerous diffuse groups of islet cells. Decided improvement followed removal of the tumor, as shown by relief from the weakness, a gain in weight of 20 pounds (9 Kg.) and elimination of the necessity for frequent feedings.

In 1937 Fanta [5] reported the case of a man aged 37 who suffered from symptoms of hypoglycemia relieved partially by the removal of a walnut-sized nodule of aberrant pancreatic tissue on the duodenum. Fanta stated that aberrant pancreatic tissue does not have the same significance with reference to hypoglycemia as does an islet adenoma.

In 1937 White and Gildea [6] reported an instance of an adenoma of islet tissue which produced a value for fasting blood sugar of 50 mg. per hundred cubic centimeters, accompanied clinically by attacks of mental confusion, headache, dizziness and diplopia and subjectively by "thickness of the tongue." The adenoma was described as a firm, calcified nodule about 12 mm. in diameter removed from the connective tissues adjacent to the posterior surface of the head of the pancreas.

To these rarely encountered cases of extrapancreatic islet tissue producing symptoms of hyperinsulinism and hypoglycemia we add a fifth, in which the sequence of events was both interesting and instructive.

Case 1.—On June 8, 1937, at 6 o'clock in the morning, the patient, a nurse, was first seen by Dr. Stockton at the request of her mother, who reported that she had "gone crazy." When examined at her home, the patient was sitting up in bed acutely upset mentally and unresponsive. The eyes were prominent and staring, with slight divergence of the eyeballs. The skin was

4. Smith, F. G.: Aberrant Pancreatic Tissue with Hyperinsulinism, J. A. M. A. **118**:454-455 (Feb. 7) 1942.

5. Fanta, E.: Hypoglykämie bei Superazidität und Nebenpankreas, Endokrinologie **19**: 34-38, 1937.

6. White, B. V., and Gildea, E. F.: Adenoma of the Pancreas and Hyperinsulinism: Report of a Case with Studies of the Effects of Emotions, of Changes in Diet and of the Administration of Acids and of Alkali on the Symptoms of Hypoglycemia, New England J. Med. **217**:307-313 (Aug. 19) 1937.

pale and moist, and the pulse rate rapid, but cranial nerves, heart and lungs were normal. During examination she fell into a deep coma and was sent to the Stanford University Hospitals in an ambulance. Five minutes after arrival at the hospital, without treatment, she was

Fig. 1 (case 1).—Cross section of the tumor mounted on a glass slide (after dehydration). Note the thin capsule and the adjacent piece of lobulated pancreatic tissue removed with the tumor (× 1).

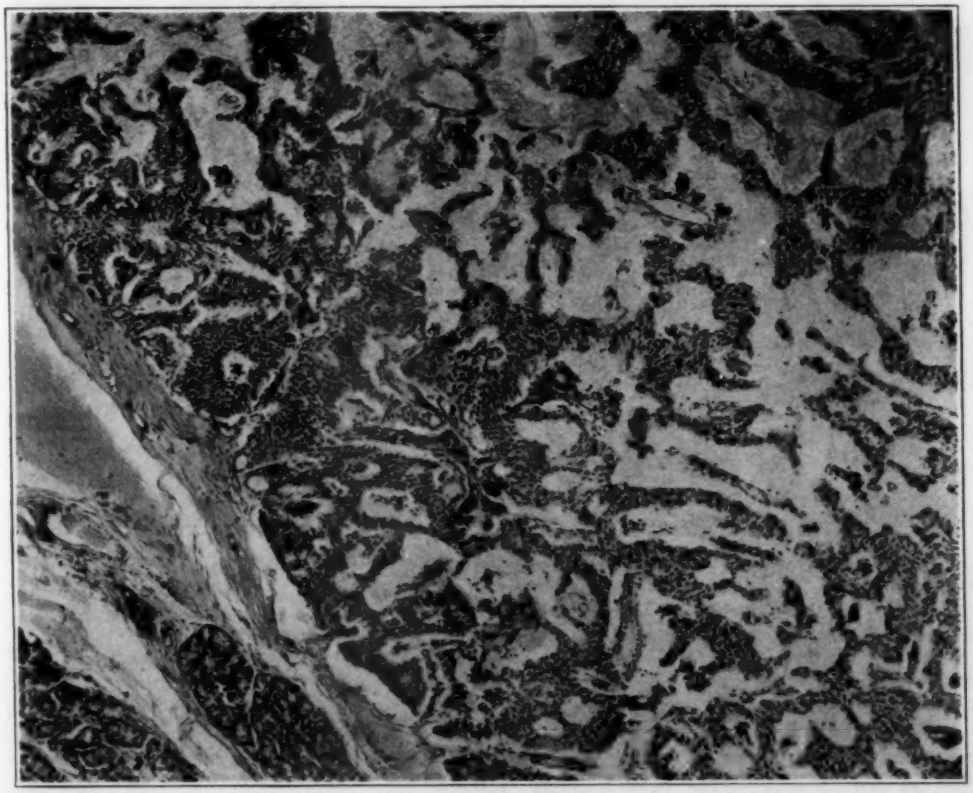

Fig. 2 (case 1).—Photomicrograph of the tumor showing the surrounding capsule and a bit of adjacent pancreas. Anastomosing narrow cords of tumor cells are separated from one another by wide vascular spaces (× 100).

perfectly conscious and apparently normal, except that she felt nervous and shaky. An immediate determination of blood sugar revealed a concentration of 48 mg. per hundred cubic centimeters.

Further questioning disclosed that in the preceding six months she had had spells of dizziness and weakness, especially before breakfast and fairly regularly at 11 a. m. and 4 p. m. These symptoms were more likely to occur after she had been eating lightly or working hard. At these times she was irritable, disoriented and capable of purposeless conduct of which she had no memory.

A second determination of blood sugar (with the patient still fasting) revealed 37 mg. per hundred cubic centimeters. The red blood cells numbered 4,650,000, the hemoglobin content was 85 per cent (Sahli method) and there were 9,800 white cells, of which 94 per cent were neutrophils, 16 per cent band forms, 78 per cent segmented cells and 5 per cent lymphocytes. The sedimentation rate was 6 mm. in an hour. The urine was normal.

At operation, performed on July 19, 1937, by Dr. P. K. Gilman, a midtransverse incision permitted a thorough and complete examination of the entire pancreas. Near the extreme end of the tail, the operator found a bluish circular tumor about 0.7 cm. in diameter, which

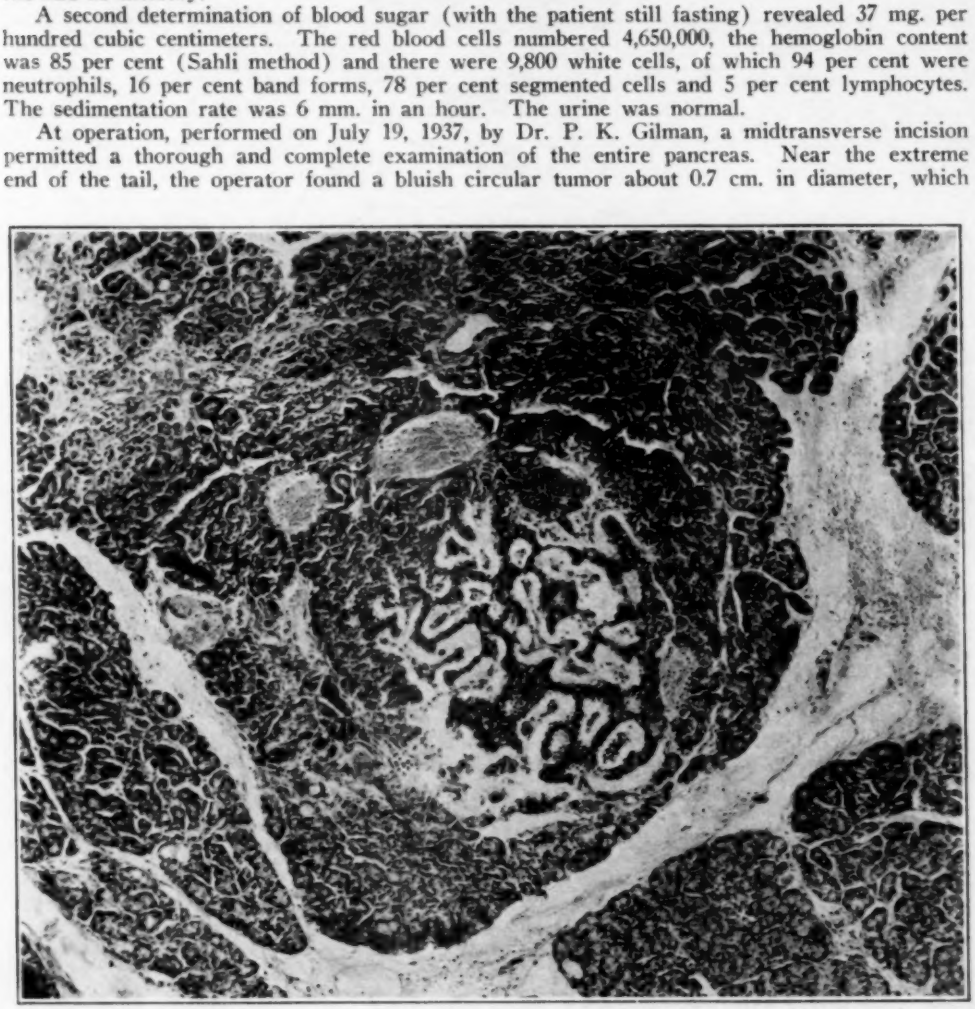

Fig. 3 (case 1).—Greatly hypertrophied islet of Langerhans in pancreatic tissue adjacent to the adenoma (× 100).

was excised with normal gland about it (fig. 1). The rent in the pancreas was resutured with catgut and a gutta-percha drain introduced into this area. An uneventful recovery followed the operation, a value for fasting blood sugar of 90 mg. per hundred cubic centimeters being recorded on September 27.

Pathologist's Report.—The gross specimen consisted of a small piece of pancreas which contained a discrete purplish nodule measuring 0.8 cm. in its greatest width. Its capsule was thin. Blood freely exuded from the freshly cut surface. Situated eccentrically was a narrow rim of pancreatic tissue (fig. 1). Histologically the tumor was completely surrounded by a thin fibrous capsule. The tumor consisted of anastomosing narrow cords of polyhedral epithelial cells. These were supported on a delicate fibrous stroma which contained numerous wide blood spaces filled with blood (fig. 2). In the adjacent pancreatic tissue scattered throughout normal-appearing acinar tissue were several islets of Langerhans, some of which showed a marked degree of hyperplasia and were several times normal size (fig. 3). The diagnosis was: adenoma of the pancreas (islets of Langerhans); focal hyperplasia of the pancreas (islets of Langerhans).

It was soon apparent that she was not absolutely well. She complained frequently of an annoying tingling in her tongue and of dizziness, followed occasionally by spells of irritability and disorientation. A value for fasting blood sugar of 54 mg. per hundred cubic centimeters was recorded on May 28, 1938, and on Jan. 18, 1939, it was 56 mg. In April 1940 she again began to have spells of fainting, with loss of consciousness for brief periods, relieved by eating. About this time menstruation became scant and irregular, the symptoms from hypoglycemia being more pronounced and more frequent just before her expected periods. Dextrose tolerance tests before and after the weekly administration of estrone (theelin), in a dose yielding 10,000 international units of estrogen, revealed temporary improvement, but her difficulties continued to increase. Attacks became as frequent as two and three times daily, varying from mere tingling in the mouth to complete unconsciousness for as long as one and one-half hours, concomitant symptoms being extreme nervousness, extreme irritability, reeling and staggering gait, profuse sweating, diplopia, headaches and convulsive movements of the arms and legs. On Sept. 22, 1941, a value for fasting blood sugar of 43 mg. per hundred cubic centimeters was recorded.

It was obvious that despite the removal of one islet tumor increasingly severe symptoms of hyperinsulinism had persisted, associated with a demonstrable hypoglycemia.

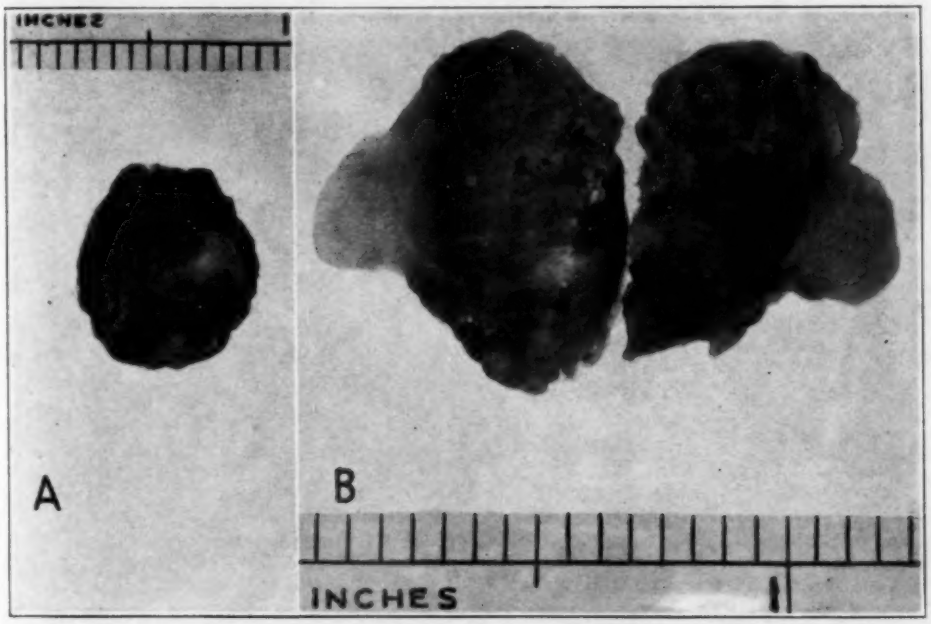

Fig. 4 (case 1).—*A*, extrapancreatic islet adenoma. Note the firm, knoblike fibrous projection (× 1½). *B*, same adenoma, except that the tumor is bisected (× 2½).

Reoperation was performed on Sept. 30, through the previous transverse incision. The entire pancreas was well mobilized except for the vessels along the upper border. No abnormal tissue was disclosed except for slight scarring in the part of the tail from which the first tumor was removed. However, in freeing the extreme tip of the tail, a rounded blue mass about 2 cm. in diameter was observed lying between the pancreas and the spleen. This was at first neglected, as it was interpreted as being an accessory spleen or a hemolymph node. When no other abnormality was disclosed in the pancreas, attention was again directed to this extrapancreatic mass. It was noted that instead of lying rather loosely embedded in fat and areolar tissue as accessory spleens usually are, the mass had apparently caused some fibroplastic reaction about it. It felt firmer than does a node or accessory spleen (fig. 4). Its removal by excision was therefore undertaken. Though liberally supplied with blood vessels, it was removed without difficulty, all bleeding points being controlled with transfixion ligatures of fine silk. The wound was closed without drainage.

Immediate cross section of the tumor disclosed pinkish white cellular tissue, which microscopically had the typical characteristics of islet tumor.

Postoperatively the concentration of sugar in the blood varied from 169 mg. per hundred cubic centimeters on Oct. 1, to 103 mg. on Oct. 15, 1941. At the time of writing, over a year later, the patient is perfectly well.

Pathologist's Report.—The gross specimen (fig. 4) consisted of an oval, encapsulated mass 1.8 by 1.5 by 1.5 cm. Section revealed medium chocolate brown, spongy tissue. The surrounding capsule of the tumor was thin and fibrous. Projecting from one aspect was a slender, grayish white elevated nodule with a broad base. It projected for 0.6 cm. and measured 0.4 cm. in width (fig. 4 *A*). The tumor appeared throughout to have been moderately vascular before it was cut into. Microscopically (fig. 5) the tumor was rather similar in structure to the first specimen (fig. 2). The capsule varied considerably in thickness and in places showed considerable hyalinization. Contained within the capsule were several small islets of tumor similar to that seen in the main mass. The tumor was composed of anastomosing columns of polygonal epithelial cells of medium size. All were markedly uniform in staining characteristics. Mitotic figures were absent. The tumor appeared benign, and the diagnosis was: adenoma of the islets of Langerhans, extrapancreatic; heterotopy (aberrant pancreatic tissue).

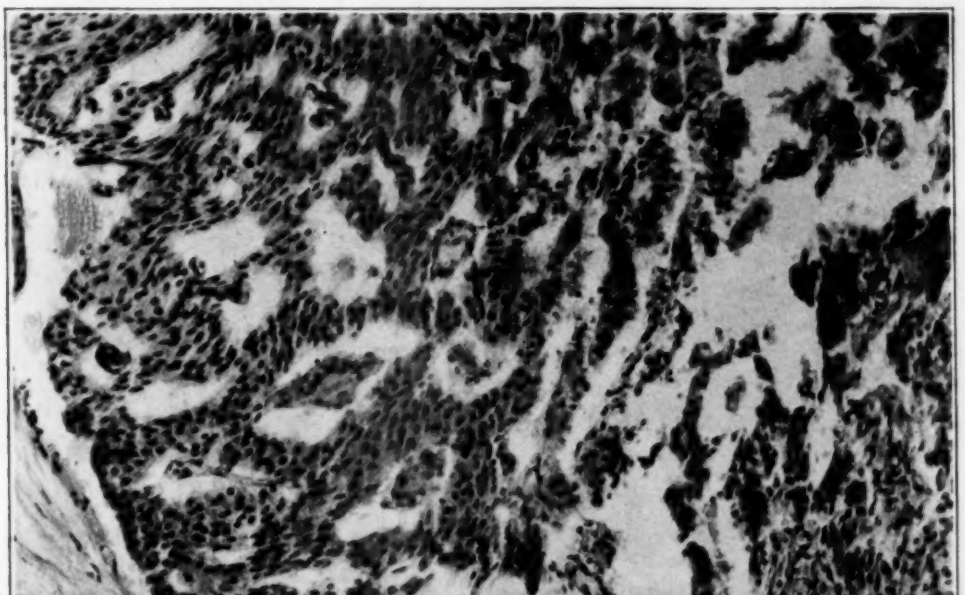

Fig. 5 (case 1).—Photomicrograph of an extrapancreatic islet adenoma. Note the similarity in structure to the pancreatic adenoma in figure 2 (× 100).

COMMENT

The lessons to be drawn from this case are obvious:

1. The presence of one islet tumor does not exclude the existence of a second. In Whipple's [7] résumé of cases of hypoglycemia to Nov. 1, 1941, multiple tumors were found in 9 of 105 cases of proved tumors of islet tissue. In 7 cases the multiple tumors were found at operation, and in 2 they were discovered at autopsy. Kalbfleisch [8] reported a case in which one adenoma was removed at operation but at necropsy two days later four other islet adenomas were uncovered. It is

7. Whipple, A. O.: Present Day Surgery of the Pancreas, New England J. Med. **226**: 513-526 (March 26) 1942.

8. Kalbfleisch, H. H.: Adenome inkretorischer Drüsen bei Hypoglykämie, Frankfurt. Ztschr. f. Path. **50**:462-477, 1937.

apparent that at operation for hyperinsulinism one cannot be entirely content with finding only one islet tumor; the entire pancreas must be exposed and searched for possible multiple islet tumors.[9] It is further apparent that even though one tumor is found within the pancreas, a careful search for a tumor outside the pancreas must be made as well, and that suspicious bluish firm nodules should be removed.

2. Hypoglycemia may be due to an islet tumor that lies wholly outside a perfectly normal-appearing pancreas. For patients who have been proved to have hypoglycemia and who exhibit Whipple's "essential triad: attacks of central-nervous-system disorder—motor, vasomotor or psychic—coming on during the fasting state; fasting blood-sugar levels of 50 mg. per cent or less; and immediate recovery from these attacks on the administration of glucose by mouth or by vein," failure to find an intrapancreatic tumor after complete and thorough search of the entire pancreas should be followed by a wide search for abnormal masses in the localities where extrapancreatic tissue is most frequently found, according to the table provided by Faust and Mudgett.

Pertinent to this discussion are the cases reviewed by David [10] in which partial or subtotal pancreatectomy was performed for hypoglycemia because no intrapancreatic islet tumor was demonstrable. In the cases in which less than half of the pancreas was removed, only 3 of the 14 patients who survived were improved. This was interpreted as emphasizing the need of a subtotal rather than partial resection of the pancreas in those cases in which no islet tumor can be found. It should be noted, however, that failure to obtain the desired effect after partial pancreatectomy in cases of hyperinsulinism characterized by the essential triad may more likely be due to failure to find the adenoma either in the remaining pancreas itself or in extrapancreatic tissues. The latter possibility may explain the following puzzling experience:

In 1928 Holman and Railsback [11] reported the removal of about two fifths of the pancreas from a patient with hypoglycemia without permanent benefit. Because of difficulties encountered in controlling bleeding from branches of the splenic artery and vein, it was suggested by Holman and Railsback that a splenectomy would facilitate pancreatectomy, a procedure which has since been adopted (Thomason [12]). Subsequently this same patient was operated on twice at the Mayo Clinic [13] for persistent hypoglycemia, first by Dr. E. Starr Judd and on a second occasion by Dr. Waltman Walters. At the third operation practically all the remaining identifiable pancreatic tissue was removed without apparent benefit to the hypoglycemia. Inasmuch as this patient, both preoperatively and postopera-

9. The outcome in case 1, as well as in some of the cases previously referred to, indicates that occasionally there exists a definite "islet imbalance." In some cases this is suggested by the presence of multiple tumors. In case 1 it was produced by the development of a second tumor and by the existence of hyperplastic islets in the resected pancreatic tissue (fig. 3). This might indicate that the islet disturbance is a hyperplastic functional response secondary to other factors. If such a hypothesis is tenable, one would expect such a factor to maintain its effectiveness and to lead, most probably, to further local adenomatous hyperplasia of the islets and even to formation of a true adenoma.

10. David, V. C.: Indications and Results of Pancreatectomy for Hypoglycemia, Surgery **8**:212-224 (Aug.) 1940.

11. Holman, E., and Railsback, O. C.: Partial Pancreatectomy in Chronic Spontaneous Hypoglycemia, with Review of Cases of Hypoglycemia Surgically Treated, Surg., Gynec. & Obst. **56**:591-600 (March) 1933.

12. Thomason, G.: Hyperinsulinism, Hypoglycemia, Subtotal Pancreatectomy, West. J. Surg. **43**:185-192 (April) 1935.

13. Carlson, L. A., and Rynearson, E. H.: An Unusual Case of Spontaneous Hypoglycemia, Proc. Staff Meet., Mayo Clin. **12**:486-490 (Aug. 4) 1937.

tively, had all of Whipple's essential triad of symptoms, the assumption is justified that he still has an islet tumor hidden away in some location where extrapancreatic tissue is occasionally found.

II. EXTRAPANCREATIC ISLET ADENOMA NOT ACCOMPANIED BY FUNCTIONAL DISTURBANCE

It is well recognized that not all hyperplasias of endocrine glandular tissues are accompanied by functional disturbance. Some adenomas, even though they morphologically mimic rather closely the structures from which they arise, are not sufficiently differentiated physiologically to assume the functions of their

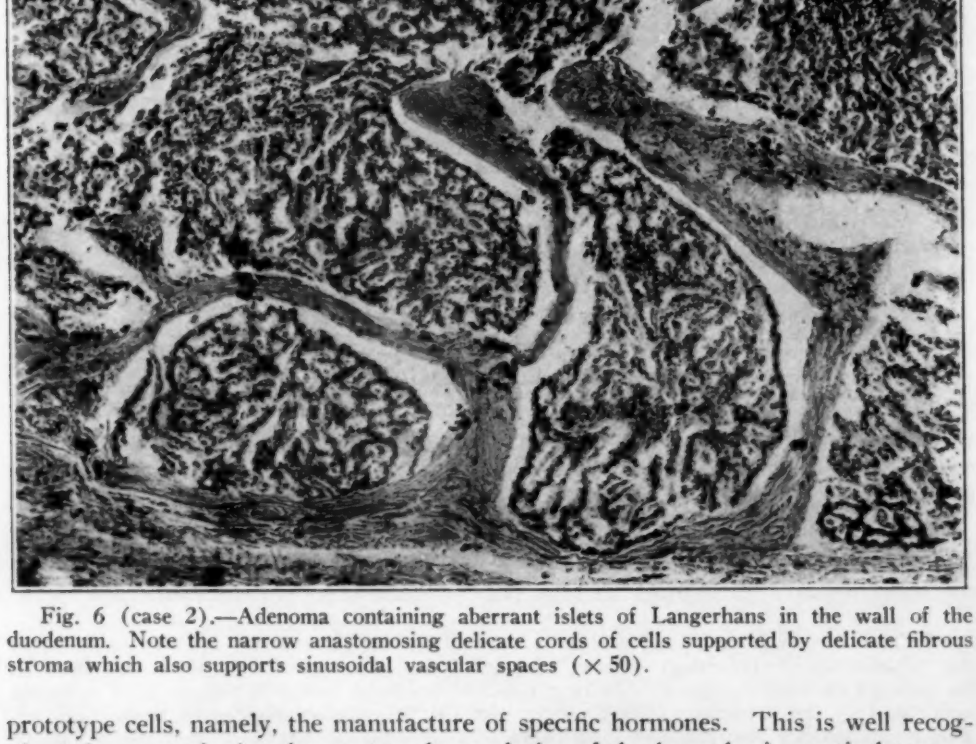

Fig. 6 (case 2).—Adenoma containing aberrant islets of Langerhans in the wall of the duodenum. Note the narrow anastomosing delicate cords of cells supported by delicate fibrous stroma which also supports sinusoidal vascular spaces (× 50).

prototype cells, namely, the manufacture of specific hormones. This is well recognized, for example, in adenomatous hyperplasias of the hypophysis, cortical tumors of the adrenal and Leydig cell tumors of the testis, as well as in granulosa cell and theca cell tumors of the ovary. Therefore, it is not surprising that one should occasionally encounter heterotopic islet tissue which does not cause hyperinsulinism.

The following case illustrates this point:

CASE 2.—Mrs. M. L., 61 years of age, entered the French Hospital in obvious shock, suffering from generalized peritonitis which had developed secondary to perforation of a diverticulum of the sigmoid colon. Her past history was irrelevant. At autopsy, aside from an acute peritonitis with 1,300 cc. of foul, seropurulent exudate, a cortical adenoma of each adrenal and an adenoma in the wall of the proximal portion of the duodenum were found. The

left adrenal contained an adenoma 0.8 cm. in width, and the right, one whose diameter was 1.0 cm. Situated in the anterior wall of the duodenum, 2.0 cm. distal to the pylorus, was a small grayish yellow submucosal nodule 0.4 cm. in width. Histologically the duodenal nodule possessed the typical structure of an islet adenoma (fig. 6).

In this case neither the heterotopic islet tissue in the duodenum nor the adrenal cortical adenomas were associated with detected physiologic disturbances.

III. CARCINOMA OF ISLETS OF LANGERHANS DEVELOPING PRESUMABLY ON THE BASIS OF AN OLD CALCIFIED ADENOMA

Most of the adenomas and carcinomas of pancreatic islet tissue have been rather small, the majority being under 2 cm. in width, and have been characterized by a rather short duration of symptoms prior to discovery. The case about to be presented is unusual and is being reported for several reasons. Prodromal symptoms existed fourteen years before the development of symptoms directly referable to hyperinsulinism. The prodromal period was followed by a two year period in which there was a rather rapid progression of the symptoms. At autopsy, a tumor 12 cm. in width containing a centrally calcified area 3.5 cm. in width was found in the tail of the pancreas. It is probable that the calcified portion represented a long-standing adenoma productive of only small amounts of insulin, thus accounting for the indefinite symptoms of the first fourteen years. It is also probable that coincidentally with the carcinomatous change in the adenoma the output of insulin increased; this would account for the appearance of symptoms clinically attributable to hyperinsulinism and the rather rapid progression of symptoms during the last two years of life. There were innumerable metastatic tumors in the liver and all of them uniformly showed a striking resemblance in structure to normal islet tissue.

Case 3.—P. C., a man 45 years of age, entered the French Hospital on June 18, 1933 and again on August 25. He died October 25.

History.—In 1917, sixteen years before his admission to the hospital, the patient began to have spells of "weakness" which would last for two to three weeks at a time and which were concurrent with the development of a sore tongue. The tongue would become red and transverse and longitudinal fissures would develop. The attacks had shown a gradual increase in severity by the end of a year, and in 1921 they were so much worse that the patient entered a hospital for a period of eleven weeks. No definite diagnosis was made, but for six years (until 1927) the patient was fairly well, except for transient weakness. The symptoms then increased in severity for two years, after which there was improvement for three years (until 1931).

In the last two years prior to the patient's admission there had been a noticeable change, characterized by a considerable increase in appetite and much greater discomfort occasioned by the spells of weakness. During these spells, which were extremely bothersome, he would become very dizzy, have blurring of vision and be unable to talk. At first the attacks were periodic, several days apart, but they became more frequent and ultimately occurred every day. (The patient had also sought outside medical care and from different physicians had received the diagnoses of "brain tumor" and "epilepsy.") After an interval the patient returned to the French Hospital and this time stated that his attacks had become as numerous as two a day, occurring before breakfast and late in the afternoon. He had discovered that by taking nourishment, such as orange juice, he could ward off an attack or obtain relief in a few minutes.

He had had the usual diseases of childhood, but no operations or accidents. He had influenza in 1918. Both parents, 3 brothers, 1 sister and 3 children were living and well. His wife had had no miscarriages or stillborn children. There was no history of gout, diabetes or cancer in the family.

Physical and Roentgen Examinations.—The patient was well developed and well nourished and weighed approximately 140 pounds (63 Kg.). The abdomen was scaphoid, and on palpation a large, tender hard mass was found in the left upper quadrant. A flat plate roentgenogram of the abdomen revealed an opaque shadow under the eleventh rib, situated in or near the tail of the pancreas.

Laboratory Studies.—Blood sugar values were as follows: on June 22, 37.5 mg. per hundred cubic centimeters; on June 27, 40.0 mg.; on July 5, 40.2 mg.; on July 11, 37.3 mg.; on August 26, 36.3 mg.; on August 28, 27.0 and 29.1 mg. before operation and 250.0 mg. during operation and after administration of 100 cc. of 10 per cent dextrose solution intravenously; on October 23, 75.0 mg.

On August 2 the basal metabolic rate was + 4 per cent. On September 16 the cholesterol content of the blood was 51.7 mg. per hundred cubic centimeters. A dextrose tolerance test carried out on August 28 revealed a fasting blood sugar of 27 mg. per hundred cubic centimeters. After one hour the value was 133.3 mg. per hundred cubic centimeters, and after two hours, 142.3 mg. A gastric analysis (Ewald) made on June 22 revealed a total acidity of 61 degrees and free hydrochloric acid, 36 degrees. Analysis of the stools on September 7, when the patient was on a Schmidt test diet, revealed no excess of fatty acids or soaps. The clinical diagnosis was hyperinsulinism and cyst of the tail of the pancreas.

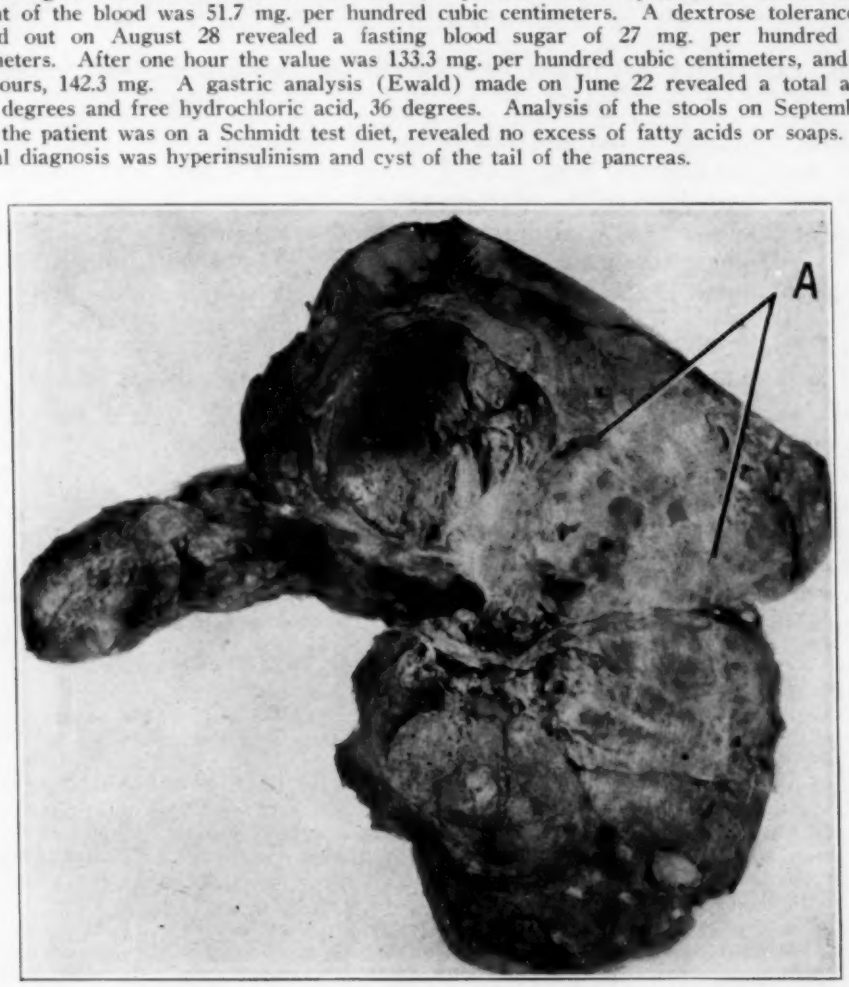

Fig. 7 (case 3).—Pancreas showing a large tumor involving the tail and the distal half. The tumor is cut in the midsagittal plane, and half is reflected downward. Centrally, outlined by "A," are faint outlines of a calcified mass. The surrounding peripheral tissue is carcinoma of islet origin (× ½).

Course.—Diagnosis was established a few days after the patient's admission to the hospital, when the blood sugar value was found to be 37.5 mg. per hundred cubic centimeters. Dextrose afforded immediate relief of symptoms. Exploratory laparotomy was performed September 28. A preoperative blood sugar value was 27.1 mg. per hundred cubic centimeters (100 cc. of 10 per cent solution of dextrose was administered intravenously during the operation). A large mass was found in the tail of the pancreas. Adjacent veins were greatly distended. On the inferior surface of the liver a hard nodular mass was found. Biopsy of both the pancreatic and hepatic tumors revealed a carcinoma of islet tissue. Postoperatively the patient was given 2,000 cc. of 10 per cent solution of dextrose intravenously every day for four days. His course was uneventful until the tenth day, when after a severe coughing spell the abdominal wound opened and allowed a partial evisceration. From this time on the patient failed to respond to therapy and became progressively weaker. On the twenty-fifth postoperative day there devel-

oped signs of extreme mental confusion which did not respond to dextrose. He lapsed into a semicomatose state and died on the twenty-seventh day. The final clinical diagnosis was carcinoma of the pancreas with metastases to the liver and hyperinsulinism.

Autopsy (Performed Three and One-Half Hours After Death).—A surgical wound in the upper portion of the right rectus muscle showed healing per primam intentionem. The peritoneum was smooth and glistening except for a few tiny adhesions near the operative sites.

A large tumor the size of a fist was present at the fossa duodenalis. At this site the peritoneum had been incised for biopsy. Veins in the ligamentum gastrocolicum were large, tortuous and filled with dark antemortem thrombus. On palpation the tumor was found to occupy the tail of the pancreas and to be rather sharply circumscribed.

The head of the pancreas and the proximal third of the corpus were normal in appearance and size (fig. 7). In the proximal portion the pancreatic duct was patent, but distally in the neighborhood of the tumor it became completely occluded. Situated in the tail was a large, slightly lobulated tumor, which measured 12 by 8 by 8 cm. Its freshly cut surface revealed lobulation with coalescent peripheral satellite nodules ranging from pale gray to yellow. In the

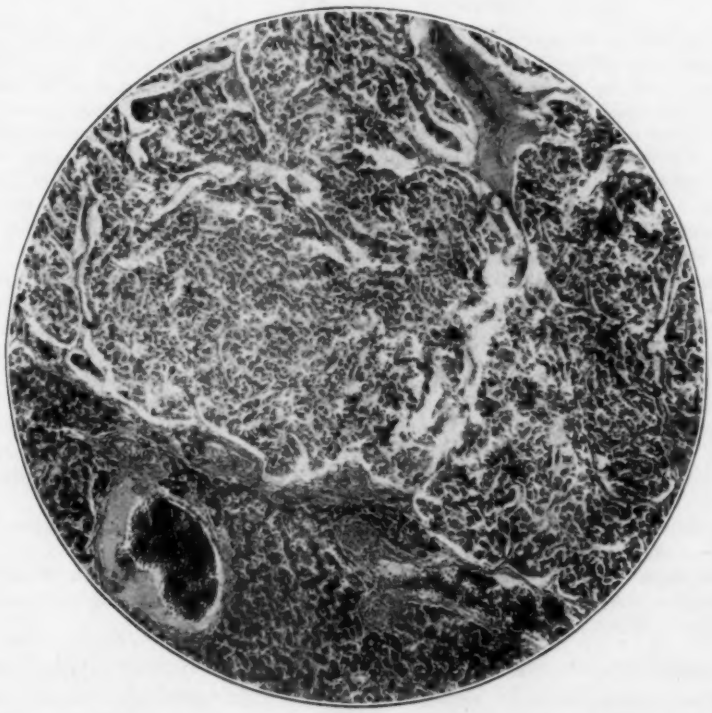

Fig. 8 (case 3).—Metastasis in the liver. Note the mimicry of islet structure by the tumor.

center was an oval area 3.5 cm. in width with slightly trabeculated stroma impregnated with calcareous material. It was fairly well circumscribed but was surrounded by tumor (fig. 7).

The liver was of medium size, measuring 27 by 21 by 8 cm. Over the convexity of the main lobe were two white nodules 4 and 5 cm. in width. Near the falciform ligament was a mass 7.5 cm. in width, and near the right coronary ligament was a mass 7 cm. in width. The smaller masses were milky white in contrast to the larger ones, which were pale yellow. On section all were found to be sharply circumscribed and to resemble closely in appearance the tumor comprising the peripheral portions of the pancreatic mass. Several smaller nodules varying from 1 to 2 cm. in diameter were scattered elsewhere throughout the parenchyma. No other metastases were found.

Both adrenals were normal in size and contained abundant cortical lipid but showed a considerable number of small nodules in the cortex.

The prostate was small, approximately two-thirds normal size. There were no foci of adenomatous hyperplasia.

Histologic Examination.—The pancreatic tumor was composed of anastomosing narrow cords of pale epithelium-like cells which were cuboidal to polygonal and of medium size. They

possessed slightly granular cytoplasm. Only a few showed hyperchromatic nuclei. Mitotic figures were extremely infrequent. A fine to moderately fibrous stroma also supported small sinusoidal vascular spaces. The resemblance of the tumor cells to those of islets of Langerhans was striking.

Section of the masses in the liver revealed tissue whose structure was essentially similar to that of the pancreatic tumor (fig. 8). The tumor was sharply demarcated from the adjoining hepatic tissue.

In the adrenal cortex there were numerous foci of adenomatous hyperplasia. Several small adenomas were contained within the adrenal capsule.

Anatomic Diagnosis.—The anatomic diagnosis was as follows: carcinoma of the islets of Langerhans; metastatic carcinoma of the liver; focal cortical hyperplasia of the adrenals; pigmentation of the skin of the hands; terminal bronchopneumonia; thrombosis of veins in the gastrocolic ligament.

IV. HYPOGLYCEMIA; APPARENTLY FUTILE EXPLORATION FOR ISLET ADENOMA; COMPLETE CURE

CASE 4.—A patient 40 years old, the mother of three children, had been troubled for two years with weakness and faintness relieved by the ingestion of sweets. In April 1937 the patient was found one morning at 7 o'clock apparently unconscious and unresponsive but was easily revived by the administration of orange juice. The next morning she was again found unconscious. The blood sugar value at this time was 33 mg. per hundred cubic centimeters. During a subsequent stay in the hospital the blood sugar values were found to lie between 40 and 60 mg. per hundred cubic centimeters with a high carbohydrate diet; between 60 and 70 mg. with a high fat diet, and between 70 and 90 mg. with a high protein diet. Further examinations disclosed a normal sella turcica, a normal gastrointestinal tract and a normal gallbladder. Pyelograms were normal, and tests of hepatic function gave normal results.

Despite an adequate and well supervised dietary regimen, the patient continued to have episodes of faintness and unconsciousness four or five times weekly. At one time her maximum period of normal comfort without food was four hours. A year later she could scarcely let two hours pass without eating. At night she found it necessary to set her alarm to be awakened every two hours for food!

On March 18, 1938, a laparotomy was performed by Holman, which revealed only normal viscera. The pancreas was separated completely from all surrounding structures except the blood vessels which entered its superior surface. All surfaces were carefully inspected and palpated for small masses, but none was discovered except a small nodule which microscopically showed chronic lymphadenitis.

Subtotal resection of the pancreas was carefully considered at the time of operation but was rejected in view of the doubtful results from such a procedure.

The patient made an uneventful recovery and has had not a single attack of unconsciousness since the operation. Although still a thin and small woman, she is eating normally and at the time of writing is driving a motor truck!

No explanation for the result can be offered. Rather apologetically it is suggested that some form of denervation was accomplished, but as the arterial supply was scarcely interrupted it is difficult to substantiate this possibility.

SUMMARY

1. Recorded in the literature are 4 cases of extrapancreatic islet adenomas producing symptoms of hyperinsulinism and hypoglycemia which were entirely controlled by removal of the extrapancreatic adenoma. To these 4 is added a fifth case in which the removal of one intrapancreatic adenoma failed to relieve the hypoglycemic symptoms, but in which the removal of a second islet adenoma in the gastrosplenic ligament produced complete cure.

In any operation undertaken in a case in which Whipple's triad of hypoglycemic symptoms is present, the possibility of multiple adenomas must be borne in mind as well as the possibility of an islet tumor lying in extrapancreatic tissue. Failure to find an intrapancreatic tumor should be followed by careful search for an islet tumor in those sites where heterotopic pancreatic tissue is frequently found.

2. Reported also is a case of heterotopic islet adenoma of the duodenum without hypoglycemic symptoms.

3. A case of islet carcinoma apparently engrafted on a calcified islet adenoma which presumably had been responsible for hypoglycemia of varying severity over a period of sixteen years is presented.

4. A bizarre case of hypoglycemia characterized by episodes of unconsciousness and blood sugar values as low as 33 mg. per hundred cubic centimeters is reported. The patient's abdomen was explored for an islet adenoma but none was found. In the course of the operation the pancreas was isolated from all surrounding structures, although its arterial supply was not interrupted. No evidences of hypoglycemia have ever again appeared. No explanation for this astonishing and unexpected result is offered.

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HEMORRHAGIC HYPOTENSION AND ITS TREATMENT BY INTRA-ARTERIAL AND INTRAVENOUS INFUSION OF BLOOD

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The suggestion was made to us by Col. Sam F. Seeley (Medical Corps, U. S. Army) that intra-arterial infusion of blood or plasma under a pressure equal to normal arterial pressure might have advantages over the conventional method of intravenous infusion in the treatment of shock. It was his view that intra-arterial infusion would elevate blood pressure rapidly, thus restoring tissue perfusion without delay; further, the exact amount of blood or plasma required to reestablish arterial pressure at any desired level would be given without the use of complex or inaccurate methods of calculation, since the intra-arterial infusion would autonomically check itself at this level. This report is based on an experimental study of Colonel Seely's suggestion.

We have also sought some test indicating the effects of hemorrhage and hypotension on the vascular system. Page [1] had shown that the pressor response to angiotonin was severely depressed by hemorrhage; subsequently we found that the response to epinephrine hydrochloride is similarly depressed. Both substances were employed as indicators of the state of vascular responsiveness.

It became necessary, once uniformity of the experimental conditions had been achieved, to devise an infusion apparatus which allowed blood to be given under controlled pressure. It was also essential that blood be withdrawn from or injected into the subject without clotting and without the use of excessive amounts of anticoagulant.

The first experiments established that animals in which a standard hypotension has been produced do not recover spontaneously. In a second series of experiments dogs were treated with either intra-arterial or intravenous infusion of all the blood removed during hemorrhage and the results compared. In a third series the two methods of infusion were compared after administration of only half of the blood removed. Finally, 3 patients suffering from traumatic shock were given plasma to demonstrate the feasibility of intra-arterial infusion in the treatment of shock in human beings.

METHODS

Dogs weighing 9 to 14 Kg. were starved for twenty-four hours and then anesthetized by the intraperitoneal injection of 30 mg. per kilogram of body weight of sodium pentobarbital. If the animals were not starved, the occurrence of abdominal distention in some dogs decreased their ability to withstand prolonged hypotension because the increased pressure against the diaphragm from the stomach and intestines handicapped respiration and cardiac function. Distention was hazardous for another reason, namely, danger of vomiting and aspiration of food during the period of recovery. It did not occur when the animals were starved for twenty-four hour periods preceding the experiment.

The experiments were performed under aseptic conditions secured by autoclaving all of the apparatus except the manometer and the pressure bulb. The apparatus used for bleeding

From the Lilly Laboratory for Clinical Research, Indianapolis City Hospital.

1. Page, I. H.: J. Exper. Med. **78**:41, 1943.

and for storing the blood and returning it to the dog by either the intravenous or the intra-arterial route is shown in the diagram (fig. 1). The femoral artery was dissected out and a glass cannula with a side arm (*A*) inserted. It was filled with heparin solution and connected to a mercury manometer (*B*) which recorded the arterial pressure on a kymograph. The side arm was connected by a short rubber tube to a glass Y tube. One limb (*C1*) was fitted with an adapter (*D*) which allowed a 10 cc. Luer syringe to be attached; the other limb (*C2*) was connected to an inverted bottle (*F*) which was suspended 12 inches (30.5 cm.) above the dog's hindleg. This bottle served as a reservoir for the blood which entered through the tube (*E*) and which could be returned to the dog through the filter (*G*). Air could escape from the bottle through a long glass tube (*I*) which extended above the surface of the blood. Pressure could be exerted on the blood within the reservoir by connecting this tube with the pressure bulb (*K*). The amount of pressure was recorded by the mercury manometer (*J*). The flow through these tubes was controlled by screw clamps (*I, II* and *V*) and by pinch clamps (*III* and *IV*). After the apparatus had been assembled the tube con-

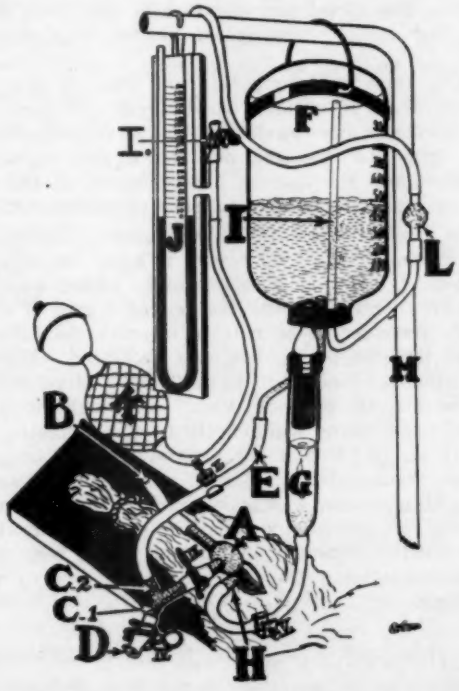

Fig. 1.—Apparatus for withdrawing blood from femoral artery and returning it either intra-arterially or intravenously. *A*, glass cannula with a side arm inserted in femoral artery; *B*, rubber tubing leading to a mercury manometer for recording arterial pressure; *C1*, limb of glass Y tube leading to adapter (*D*); *C2*, limb of Y tube connected by rubber tube (*E*) with blood reservoir (*F*); *D*, adapter for connecting 10 cc. Luer syringe; *G*, outlet from blood reservoir through a steel cloth filter; *H*, tube from blood reservoir connected to a cannula in femoral vein for venous return of blood; tube *H* connected to limb *C2* of glass Y tube for intra-arterial infusion; *I*, air inlet in blood reservoir; *J*, mercury manometer for recording pressure within blood reservoir during intra-arterial infusion; *K*, pressure bulb for increasing pressure within blood reservoir; *L*, cotton filter for air entering blood reservoir; *M*, iron standard for supporting apparatus; *I*, clamp closing air inlet during intra-arterial infusion; *II* and *V*, screw clamp on tubes leading to and from blood reservoir; *III* and *IV*, pinch clamps on side arm of cannula and limb of Y tubing leading to adapter.

necting the side arm of the cannula to the reservoir was filled with 10 per cent solution of sodium citrate.

Bleeding was done with this apparatus by opening clamp *I* on the air vent, closing clamp *V* on the outflow tube of the reservoir, closing clamp *IV* on the limb of the Y tube and

removing clamp *III* on the side arm of the cannula. The rate of flow was controlled by adjusting clamp *II* on the tube between the glass Y and the reservoir. Bleeding was stopped by closing this clamp.

Ten cubic centimeters of 10 per cent solution of sodium citrate was injected through tube *E* into the reservoir before the hemorrhage was started. This was sufficient to prevent clotting of the blood removed during the initial hemorrhage. Five cubic centimeters of sodium citrate solution was then added for every 100 cc. of blood received during the course of the experiment.

Since most of the heparin solution had been carried from the arterial cannula to the reservoir during the hemorrhage, clotting occurred within the cannula unless the anticoagulant was quickly replaced after each hemorrhage. After the initial hemorrhage, heparin was injected into the arterial cannula from the Luer syringe attached to the adapter *D* by removing clamp *IV* on the limb of the Y tube. When sufficient anticoagulant had been injected, clamp *III* was replaced on the side arm of the cannula.

It was equally important to prevent clotting of blood in the tube leading to the reservoir from the glass Y. Citrated blood was withdrawn from the reservoir into the syringe attached at *D* by opening clamp *II*. This blood was drawn back and forth through this tube until it was thoroughly citrated. Five cubic centimeters of citrated blood was left in the syringe, and clamp *IV* was replaced.

Bleeding was resumed by removing clamp *III* from the side arm and adjusting clamp *II*. After each hemorrhage the 5 cc. of citrated blood which had been left in the syringe was injected into the arterial cannula as anticoagulant instead of heparin solution.

The external jugular vein was dissected out and ligated cephalad. A no. 12 French rubber catheter was inserted until the tip was approximately at the level of the atrium. It was filled with heparin solution and connected to a water manometer.

Method of Bleeding to Produce Sustained Hypotension.—Bleeding was done in stages as follows: An initial large volume of blood, equivalent to 2 per cent of the animal's body weight, was withdrawn in a period of less than three minutes. After partial recovery portions of 100 cc. each were withdrawn at intervals until the desired degree of hypotension was attained. When the arterial pressure remained at 50 mm. of mercury the volume of each hemorrhage was reduced to 50 cc. and the rate of bleeding was decreased. When the pressure reached 40 mm. of mercury the volume was reduced to 10 to 20 cc. of blood slowly withdrawn.

With some practice the arterial pressure could be brought to and kept at 30 mm. of mercury in the majority of experiments within forty to sixty minutes. In some it was necessary to withdraw 10 or 15 cc. of blood if the arterial pressure began to rise, and in other experiments if the pressure declined below 30 mm. of mercury it was necessary to reinfuse small quantities of blood. Hypotension was maintained for forty minutes before the vascular responsiveness to angiotonin or epinephrine was tested. The maximum amount of blood removed was 7.2 per cent and the minimum 3.1 per cent of the body weight, and the duration of the periods of sustained hypotension (30 to 40 mm. of mercury) varied from thirty-three to one hundred and six minutes.

CRITERIA USED TO INDICATE THE EFFECTS OF PROLONGED HYPOTENSION

Possibly because of differences in age, state of nutrition, hydration and breed among the dogs, maintenance of arterial pressure at 30 mm. of mercury for the same length of time did not always have the same effect on survival. The pressor responses to angiotonin and epinephrine were therefore used as additional criteria in estimating the effect of prolonged hypotension.

The angiotonin solution was standardized so that 0.1 cc. gave the same rise in arterial pressure in a pithed cat as 0.002 mg. of epinephrine hydrochloride. In each experiment it was administered before bleeding in order to determine the amount necessary to produce a rise of at least 16 mm. of mercury. For most dogs 0.2 cc. was sufficient, but for some 0.4 cc. or even 1.0 cc. was needed.

After arterial pressure had been maintained at 30 mm. of mercury for forty minutes, the same dose of angiotonin was administered as had been given in the prehemorrhagic stage. If the response had been reduced to less than 8 mm. of mercury treatment was started, but if it had not been sufficiently diminished hypotension was continued, and the angiotonin injection was repeated at intervals of from ten to fifteen minutes.

During the course of these experiments it was found that prolonged hypotension also diminished the pressor response to 0.1 to 0.2 cc. of a 1:10,000 solution of epinephrine hydrochloride. In 4 experiments the hypertensive effects of angiotonin and epinephrine hydrochloride paralleled one another. Because of the difficulty of obtaining sufficient angiotonin, epinephrine hydrochloride was used in many of the experiments.

METHOD OF TREATMENT OF POSTHEMORRHAGIC HYPOTENSION

In those experiments in which the intra-arterial route was used, the rubber tube from the filter *G* (fig. 1) was placed on a limb of the glass Y tube *C1*. This permitted the blood to flow from the reservoir through the filter and into the arterial cannula in the femoral artery. Tightening clamp *I* closed the air vent, and compressing the bulb *K* raised the pressure in the reservoir to 50 mm. of mercury. Infusion began when clamps *V* and *III* were opened.

As the systemic arterial pressure increased, the rate of infusion decreased until the inflow became intermittent and then stopped altogether. When this occurred the pressure within the reservoir was raised to 80 mm. of mercury and infusion resumed. In some experiments a pressure of 120 mm. of mercury was necessary to complete the infusion. The average rate of administration of blood was 48 cc. per minute. Intravenous infusion was accomplished by connecting the tube from the filter *G* to a glass cannula in the femoral vein *H*.

In some experiments a rise of more than 5 cm. of water in venous pressure served as a sign for reducing the infusion rate. In other experiments the venous pressure was not used as a guide because experience showed that a rate of 100 and 200 drops of blood per minute was below the limit at which venous pressure rose to alarming heights.

After infusion the artery and veins were ligated, the cannulas removed and the wounds sprayed with sulfathiazole powder.

TABLE 1.—*Sustained Hypotension—Not Treated*

Experiment No.	Hematocrit Value, Mm.	Arterial Pressure Before Bleeding, Mm. Hg	Blood Removed, Cc.	Blood Removed, per Cent of Body Weight	Time for Hemorrhage, Minutes	Arterial Pressure After Hemorrhage, Mm. Hg	Survival, Minutes	Hematocrit Value Before Death, Mm.
1	28	120	330	3.9	25	34	46	20
2	55	144	430	4.5	40	30	260	45
3	55	160	595	5.9	53	40	123	41
4	34	130	370	3.3	55	35	55	33
5	35	160	280	4.0	17	20	35	35
6	38	124	470	3.9	18	20	20	
7	46	156	810	5.6	20	30	35	
8	32	138	550	5.0	50	34	67	27

RESULTS

Sustained Hypotension Not Treated.—Eight dogs were bled as described until the arterial pressure was reduced to 30 or 50 mm. of mercury, and the duration of survival was noted. No effort was made to maintain the pressure at this level by reinjecting blood when it fell below 30 mm. of mercury. The longest period of survival was two hundred and sixty minutes and the shortest twenty minutes (table 1). Hematocrit determinations made when death seemed imminent showed an average reduction of 8 per cent in the volume of packed cells.

Further evidence of the narrow margin of safety which existed when this level of hypotension was maintained is the death of dogs during experiments in which treatment was contemplated but in which it was never begun because the dogs died before the minimum of forty minutes of hypotension had been completed or before the pressor response to angiotonin was reduced by less than 10 mm. of mercury.

Sustained Hypotension Treated by the Intra-Arterial Administration of All the Blood Removed.—After the period of hypotension, all of the blood that had been removed from the dog was returned by the intra-arterial method. The infusion was started by exerting 50 mm. of mercury pressure on the blood in the reservoir. Its effect on arterial pressure is exemplified in figure 2. One hundred to 175 cc. of blood usually entered the artery in the first two or three minutes,

and at the end of this time arterial pressure had increased sufficiently to exceed the infusion pressure of 50 mm. of mercury and stop the inflow of blood. After an interval of a few minutes infusion was resumed by increasing the pressure within the reservoir to 80 mm. and then to 120 mm. of mercury.

There were 12 experiments in this series and all of the animals but 1 (experiment 12, tables 2, 3, 4 and 5) survived.

When dogs with hypotension were treated by the intra-arterial method, the cardiovascular system usually failed to respond adequately if a pressure of more than 50 mm. of mercury was used in the blood reservoir to start the infusion. This failure was indicated by a sharp rise in intrathoracic venous pressure, of 10 to 15 cm. of water, and death ensued. Of 32 dogs in which the initial infusion pressure was 50 mm. of mercury the cardiovascular system failed to respond in only 2. To the first of these 400 cc. of blood was administered in seven minutes (experiment 12, tables 2 and 3), and the venous pressure increased 12 cm. of water but the arterial pressure did not rise above 50 mm. of mercury. The animal died within ten minutes after infusion was completed. To the second dog (no. 43, tables 6 and 7) 275 cc. of blood, which was one half of the blood removed,

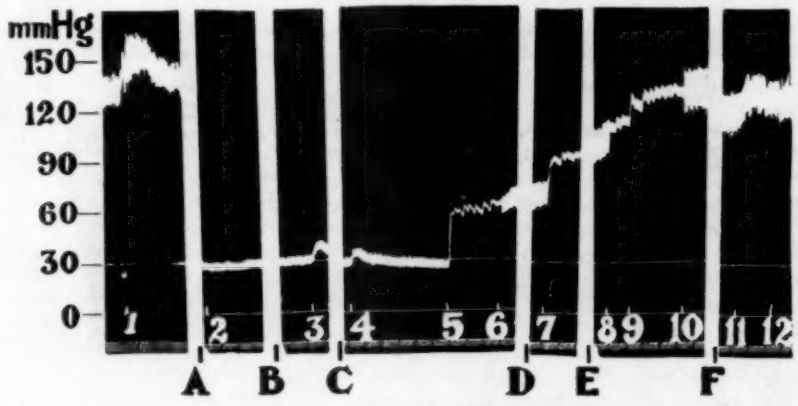

Fig. 2.—Experiment in which sustained posthemorrhagic hypotension was treated by intra-arterial infusion of all of the blood removed. The dog weighed 15 Kg. (experiment 11, tables 2 and 3). *1*, 0.2 cc. of angiotonin; *A*, space represents an interval of sixty minutes during which 900 cc. of blood was removed by intermittent bleeding; *2*, arterial pressure of 30 mm. of mercury—sustained hypotension begins; *B*, space represents thirty minutes of sustained hypotension; *3*, 0.2 cc. of angiotonin administered after thirty-six minutes of sustained hypotension; *C*, space represents five minutes of continued hypotension; *4*, 0.2 cc. of angiotonin; *5*, intra-arterial infusion started with a pressure of 50 mm. of mercury in the blood reservoir; *6*, infusion stopped by rising arterial pressure; 110 cc. of blood had been infused within three minutes; *D*, space represents interval of four minutes; *7*, infusion started again by increasing pressure within the reservoir to 80 mm. of mercury; *E*, space represents an interval of nine minutes during which infusion was continued; *8*, rising arterial pressure stopped infusion after 460 cc. of blood had been administered; *9*, infusion continued by raising pressure within the reservoir to 120 mm. of mercury; *10*, infusion of 800 cc. of blood completed in twenty-one minutes; *F*, space represents an interval of ten minutes; *11*, 0.2 cc. of angiotonin administered twelve minutes after infusion; *12*, venous pressure had been restored to prehemorrhagic level (maximum rise during infusion, 4 cm.).

was administered in five minutes. The venous pressure rose 13 cm. of water, and the dog died within two minutes after the infusion was stopped.

The effect of intra-arterial infusion on venous pressure was unpredictable. It could not be correlated directly with the rate of infusion. Thus, 68 cc. per minute for seven minutes caused a rise of only 2 cm. of water (experiment 25,

table 5) while 18 cc. per minute for thirty-three minutes raised the venous pressure 14 cm. of water (experiment 20, table 5). In general, the greatest change in the venous pressure was observed in those experiments in which large volumes of

TABLE 2.—*Production of Sustained Hypotension to Be Treated by Infusion of All of the Blood Removed (See Table 3)*

	Prehemorrhagic Period				Period of Intermittent Bleeding				Period of Hypotension			
Experiment No.	Weight, Kg.	Hematocrit Value, Mm.	Arterial Pressure, Mm. Hg	Response to 0.2 Cc. Angiotonin or 0.1 Cc. of Epinephrine Hydrochloride, Mm. Hg	Blood Removed, Cc.	Blood Removed, per Cent Body Weight	Change in Venous Pressure, Cm. Water	Time to Reach Sustained Hypotension, Minutes	Arterial Pressure: Maximum, Mm. Hg	Arterial Pressure: Minimum, Mm. Hg	Duration, Minutes	Response to Angiotonin or Epinephrine at End of Period
					Dogs Recovered After Intra-Arterial Infusion							
9	10	30	138	36	605	6	—3	27	40	28	73	0
10	9.3	36	122	22	450	4.8	—2.5	22	38	24	97	—2
11	15	40	122	22	900	6	0	59	40	34	55	6
					Dogs Died After Intra-Arterial Infusion							
12	10	52	156	22	400	4	—7	38	30	20	68	0
					Dogs Recovered After Intravenous Infusion							
13	10.8	42	146	30	540	5	—2	18	46	38	70	10
14	14	53	144	20 (Epinephrine)	600	4.2	2	30	40	36	80	10 (Epinephrine)
15	13.3	34	150	40	728	5.5	—1.2	37	42	34	43	2
16	10.2	40	122	36	625	6.1	—3.5	46	38	34	53	4
17	10.5	46	126	26	640	6.0	—3.5	50	42	38	60	4
18	10	44	108	28	610	6.1	—2.2	71	42	30	44	8
					Dog Died After Intravenous Infusion							
19	11.8	50	160	18	450	3.7	—2.0	50	52	38	65	0

TABLE 3.—*Sustained Hypotension Treated by the Infusion of All of the Blood Removed*

	Period of Infusion				After Treatment	
Experiment No.	Arterial Pressure Infusion Begins, Mm. Hg	Blood Infused, Cc.	Time of Infusion, Minutes	Blood Infused per Minute, Cc.	Arterial Pressure, Mm. Hg	Response to 0.2 Cc. Angiotonin or 0.1 Cc. of Epinephrine Hydrochloride Solution, Mm. Hg
		Dogs Recovered After Intra-Arterial Infusion				
9	28	535	8	66	134	8
10	24	450	20	24	118	16
11	34	800	20	40	126	10
		Dog Died After Intra-Arterial Infusion				
12	22	400	7	57	0	
		Dogs Recovered After Intravenous Infusion				
13	36	600	47	12	138	(Epinephrine)
14	40	550	75	7.3	116	
15	36	700	51	13	114	24
16	34	610	35	17	118	38
17	38	625	35	17	116	36
18	30	590	43	13	106	42
		Dog Died After Intravenous Infusion				(Angiotonin)
19	38	425	55	7.7	102	0

blood quickly entered the circulation without increasing arterial pressure over 50 mm. of mercury.

Sustained Hypotension Treated by Intravenous Infusion of All of the Blood Removed.—In 7 experiments (tables 2 and 3) sustained hypotension was treated

by returning intravenously all of the blood removed. The rate of infusion was governed by the intrathoracic venous pressure. If it suddenly rose more than 5 cm. of water the flow was reduced or stopped until it became stabilized. The

TABLE 4.—*Production of Two Periods of Sustained Hypotension in the Same Dog, the First to Be Treated by the Intra-Arterial and the Second by the Intravenous Method*

			Prehemorrhagic Period			Period of Intermittent Bleeding				Period of Hypotension			
Experiment No.	Method of Infusion	Weight, Kg.	Hematocrit Value, Mm.	Arterial Pressure, Mm. Hg	Response to 0.2 Cc. Angiotonin, Mm. Hg	Blood Removed, Cc.	Blood Removed, per Cent Body Weight	Change in Venous Pressure, Cm. Water	Time to Reach Sustained Hypotension, Min.	Arterial Pressure		Duration, Min.	Response to 0.2 Cc. Angiotonin at End of Period
										Maximum, Mm. Hg	Minimum, Mm. Hg		
20	Arterial	10.3	..	136	20	600	5.8	—11	42	36	24	68	0
	Venous	10	38	130	26	595	5.9	— 3	46	30	28	78	6
21	Arterial	14.2	50	160	16	660	4.7	— 2.0	35	46	30	52	0
	Venous	12.0	40	118	14	665	5.5	— 4.0	18	50	34	55	2
22	Arterial	14.6	42	158	18	520	3.2	— 5.0	32	40	20	58	0
	Venous	13	40	136	16	575	4.1	— 2.0	25	44	28	60	0
23	Arterial	11.7	34	152	34	650	5.5	— 2.5	33	42	16	62	0
	Venous	11	50	178	18	640	5.4	— 2.5	38	36	16	69	0
24	Arterial	10	30	130	20	600	6	— 4	26	38	18	114	0
	Venous	10	45	132	12	472	4.7	— 3	29	32	28	46	0
25	Arterial	12.5	32	142	18	500	4	— 2.2	26	40	30	38	0
	Venous	10	30	118	28	300	3	— 2.0	18	30	26	45	8
26	Arterial	13.5	44	174	16	905	6.6	— 4.0	60	46	28	36	0
	Venous	11.6	39	150	20	350	3.0	— 2.5	20	40	26	64	10
27	Arterial	10.8	49	120	28	570	5.3	— 5.0	38	38	32	68	—12
	Venous	10.9	38	130	18	600	5.5	— 2.0	28	40	30	68	0

TABLE 5.—*Sustained Hypotension Treated by Intra-Arterial and Intravenous Method in the Same Dog*

		Period of Infusion				After Treatment		
Experiment No.	Method of Infusion	Arterial Pressure Before Infusion, Mm. Hg	Blood Infused, Cc.	Time for Infusion, Minutes	Blood Infused per Minute, Cc.	Arterial Pressure, Mm. Hg	Change in Venous Pressure, Cm. Water	Response to 0.2 Cc. Angiotonin, Mm. Hg
20	Arterial	26	600	33	18.1	130	14	11
	Venous	28	595	93	6.4	132	3	16
21	Arterial	30	500	13	38.4	110	6	12
	Venous	36	665	124	4.5	134	4	10
22	Arterial	32	500	27	18.0	122	6	12
	Venous	28	575	49	11	110	1.5	6
23	Arterial	30	580	10	58	118	9	18*
	Venous	26	170	15	11	0	5	
24	Arterial	18	530	27	19	122	6	12*
	Venous	28	192	28	6.8	0	10	
25	Arterial	30	480	7	68	122	2	18
	Venous	28	250	27	9.2	70	2	10
26	Arterial	28	600	21	28	130	5	22
	Venous	28	370	66	5.6	100	2.5	18
27	Arterial	32	500	14	35.7	120	11.0	
	Venous	30	600	100	6.0	110	2.0	8

* Dogs died during intravenous infusion.

average rate of flow was 12 cc., which was approximately one-fourth the rate of the intra-arterial infusion.

The arterial pressure rose slowly (fig. 3), but the level of pressure at the end was the same as after an intra-arterial infusion. The average time for the completion of the infusion was forty-nine minutes. Six dogs recovered, but the

seventh died one hour after the infusion. In the last-mentioned animal the arterial pressure at the end of the infusion was 102 mm. of mercury but began to decline as soon as the infusion stopped. Postmortem examination revealed typical visceral hemorrhages.

TABLE 6.—*Production of Sustained Posthemorrhagic Hypotension to Be Treated by Returning One Half of Blood Removed*

		Prehemorrhagic Period				Period of Intermittent Bleeding				Period of Hypotension				
				Response to 0.2 Cc. Angiotonin or 0.1 Cc. of Epinephrine Hydrochloride (1:10,000)						Arterial Pressure			Response to 0.2 Cc. Angiotonin or 0.1 Cc. of Epinephrine Hydrochloride Solution After Hypotension	
Experiment No.	Weight, Kg.	Hematocrit Value, Mm.	Arterial Pressure, Mm. Hg	Angiotonin	Epinephrine	Blood Removed, Cc.	Blood Removed, per Cent Body Weight	Change Venous Pressure, Cm. Water	Time to Reach Sustained Hypotension, Min.	Maximum, Mm. Hg	Minimum, Mm. Hg	Duration of Hypotension, Min.	Angiotonin	Epinephrine
Dogs Recovered After Intra-Arterial Infusion														
28	14.2	26	158	14	18	545	3.8	—1.0	19	40	20	54	2	6
29	11.6	38	160	18	38	700	6	0	83	34	28	59	8	12
30	12.6	44	150	..	54	725	5.6	—6.0	44	40	30	106	..	8
31	9.5	37	144	..	28	578	6	—2.5	42	40	26	56	..	2
32	14	42	166	..	38	510	4	—3.0	55	36	28	65	..	0
33	9.4	40	142	..	44	605	6.4	—4.2	36	36	24	33	..	0
34	9	36	138	..	52	480	5.3	—3.0	34	38	28	34	..	2
35	12.1	40	118	..	26	670	5.5	—2.5	53	36	30	69	..	8
36	11.5	50	140	..	36	625	5.4	—3.0	92	36	32	62	..	—8
37	12.0	44	140	..	34	632	5.2	—1.6	31	42	36	96	..	10
38	13.9	43	164	..	74	875	6.3	—2.3	115	36	34	33	..	0
39	12.5	47	194	..	22	610	4.8	—3.2	35	36	26	35	..	6
40	11.5	41	156	..	34	410	3.6	—2.5	50	36	26	46	..	4
41	10	46	148	..	80	525	5.2	—4.0	42	38	24	65	..	6
42	10.2	44	156	..	34	615	6	—3.0	57	38	36	40	..	2
Dogs Died Within Twelve Hours After Intra-Arterial Infusion														
43	11	46	180	26	50	550	5	—1.5	45	38	30	45	4	6
44	12	38	148	16	..	560	4.6	—5	40	46	28	65	4	..
45	11.2	55	138	..	46	760	6.7	—5.5	59	32	26	40	..	4
46	14.2	42	158	..	38	760	5.3	—8.0	43	36	30	71	..	12
47	11.6	36	182	..	18	500	4.3	—6.8	26	36	30	67	..	2
Dogs Recovered After Intravenous Infusion														
48	12.6	46	140	..	36	910	7.2	—5	64	34	28	40	..	0
49	14.1	42	148	..	44	850	6.1	—1.5	35	34	28	74	..	6
50	9.6	38	150	52	..	635	6.6	—4	57	46	30	63	8	..
51	12	50	146	..	30	610	5	—2.4	43	38	28	46	..	6
52	10.5	40	126	..	44	400	4	—3	53	40	28	39	..	10
53	9.9	46	150	..	50	500	5	—5	63	38	26	57	..	6
Dogs Died After Intravenous Infusion														
54	12.3	42	138	30	30	834	6	0	83	34	28	59	8	12
55	10.5	44	138	..	40	580	5.6	—6	74	40	28	42	..	0
56	11	40	146	..	30	445	4	—1.7	41	36	28	41	..	8
57	13.4	36	120	..	28	700	5.2	—5	62	46	26	57	..	6
58	8.5	36	134	..	34	500	5.8	—3.0	77	30	20	40	..	0
59	12.4	44	160	..	26	620	5	—5.5	42	36	26	37	..	0
60	11.9	40	154	..	32	615	5	—4.7	24	46	20	41	..	8
61	10.3	36	130	..	44	420	4.2	—0.8	47	30	24	40	..	0
62	11.4	42	156	..	32	575	5.4	—3.5	34	38	24	44	..	4
63	9.3	44	136	..	42	360	4	—3.0	33	34	24	43	..	8
64	11.9	46	170	..	36	615	5.1	—4.6	58	30	26	41	..	6
65	9.3	55	176	..	26	472	5	—1.5	50	34	26	45	..	6
66	10.5	31	130	..	14	550	5.3	0	38	36	26	43	..	2
67	13.9	53	182	..	44	894	6.4	—4.5	66	32	24	40	..	6

Venous pressure was increased by a smaller volume of blood and a much slower rate of infusion when blood was given intravenously than when it was given by the intra-arterial route.

Comparison of Intra-Arterial and Intravenous Methods of Treatment in the Same Dog When All of the Blood Removed Was Returned.—Because of the wide variations among most dogs, a more equitable basis for the comparison of these two methods was obtained by subjecting a dog which had recovered from sustained

hypotension treated by intra-arterial infusion to a second period of hypotension treated by the intravenous method. Eight dogs were treated in this manner (tables 4 and 5). An interval of at least two or three weeks elapsed between the first and the second period of hypotension. Every effort was made to

TABLE 7.—*Sustained Hypotension Treated by Infusion of One Half of Blood Removed*

	Period of Infusion				After Treatment				
					Arterial Pressure		Response to 0.2 Cc. of Angiotonin or 0.1 Cc. Epinephrine Hydrochloride Solution (1:10,000)		
Experiment No.	Arterial Pressure When Infusion Began, Mm. Hg	Blood Infused, Cc.	Time of Infusion, Minutes	Blood Infused per Minute, Cc.	At End of Infusion, Mm. Hg	1 Hour After Infusion, Mm. Hg	Angiotonin	Epinephrine	Hematocrit Value, Mm.
				Dogs Recovered After Intra-Arterial Infusion					
28	30	270	9	30	88	90	18	22	..
29	28	355	10	35	120	122	12	22	..
30	30	360	14	25	116	120	..	30	48
31	26	285	12	23	96	110	..	26	42
32	28	250	10	25	90	106	..	18	46
33	24	300	12	25	122	90	..	16	46
34	26	235	8	29	130	132	..	26	38
35	30	335	8	41	72	94	..	30	32
36	32	310	8	38	90	94	..	20	48
37	36	315	9	35	98	120	..	18	46
38	28	440	14	31	100	130	..	28	46
39	24	305	15	20	146	160	..	20	42
40	26	200	5	40	96	76	..	26	40
41	24	260	6.5	43	138	140	..	28	48
42	28	305	7	43	100	126	..	20	44
				Dogs Died Within Twelve Hours After Intra-Arterial Infusion					
43	28	275	5	55	60	0	0	0	*
44	30	255	8	31	86	110	0	..	42†
45	26	375	8	45	90	98	..	12	56‡
46	28	380	11	34	86	112	..	28	44§
47	30	250	5	50	110	102	..	6	46¶
				Dogs Recovered After Intravenous Infusion					
48	28	455	78	5.7	102	106	..	8	56
49	28	435	58	7.5	140	132	..	32	42
50	30	315	46	7.0	122	136	32	..	50
51	28	309	36	8.5	90	118	22	30	46
52	28	200	16	12.5	108	94	..	20	46
53	26	250	45	5.5	110	112	..	26	50
				Dogs Died Within Twelve Hours After Intravenous Infusion					
54	28	416	33	12	100	72	16	14	#
55	28	290	28	10	110	100	..	0	#
56	28	225	47	4.8	76	90	..	30	36‖
57	30	335	35	9.5	138	100	..	12	46#
58	20	250	30	8	0	0	..	..	34#
59	20	310	45	7.0	120	90	..	10	48#
60	20	310	22	14	70	70	..	12	4C#
61	24	210	31	6.8	82	86	..	30	‖
62	24	285	19	15	82	96	20	40	3C#
63	24	180	25	7.2	108	90	..	18	46‖
64	26	300	36	8.5	120	84	..	16	50‖
65	26	235	15	15	120	126	..	6	50‖
66	26	270	11	24	108	84	..	10	27#
67	24	437	13	33	122	122	..	8	56‖

* Dog survived thirty minutes after infusion.
† Dog survived eight hours after infusion.
‡ Dog survived five hours after infusion
§ Dog survived twelve hours after infusion.
# Dog survived less than six hours after infusion.
‖ Dog survived twelve hours after infusion.
¶ Dog survived three hours after infusion.

reproduce in the second period the same conditions that had existed in the first. The duration of each period was determined by the time required to reduce the pressor response to angiotonin to less than 10 mm. of mercury. In all but 2 experiments the average duration of the second hypotensive period was six minutes more than the first.

All 8 dogs receiving the intra-arterial infusion recovered. Two dogs failed to do so when treated by the intravenous method, and in both of these death occurred before all of the blood removed could be returned.

The first dog which died during intravenous infusion (experiment 23, tables 4 and 5) had received 580 cc. of blood intra-arterially in ten minutes with no apparent ill effects, but only 170 cc. of the 640 cc. of the blood removed could be returned during fifteen minutes of intravenous infusion. The second dog (experiment 24, tables 4 and 5) had received 530 cc. of blood intra-arterially in twenty-seven minutes and recovered, but death occurred after 192 cc. of the 472 cc. of blood removed had been infused intravenously in twenty-eight minutes. The intravenous infusion could not have been administered more rapidly, because as it was venous pressure had suddenly risen 10 cm. of water, a rise which we took to be a sign of impending cardiac failure. In both dogs all the blood removed had been infused intra-arterially in less time than was now required for incomplete and ineffective intravenous infusion. Further, as we shall see, the proportion of

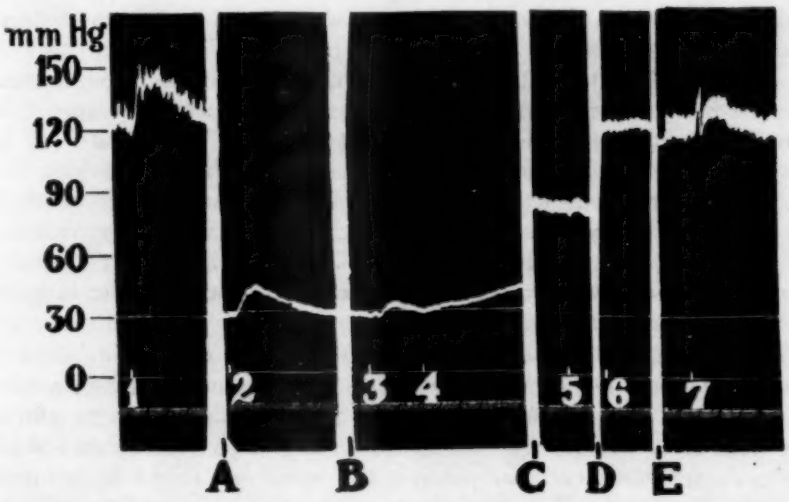

Fig. 3.—Experiment in which sustained posthemorrhagic hypotension was treated by intravenous administration of all of the blood removed. The dog weighed 10 Kg. (experiment 20, tables 4 and 5). *1*, 0.2 cc. of angiotonin; *A*, space represents an interval of eighty-four minutes during which arterial pressure was reduced to hypotensive level by withdrawal of 595 cc. of blood in forty-six minutes and hypotension was maintained for thirty-eight minutes; *2*, 0.22 cc. of angiotonin administered after thirty-eight minutes of hypotension; *B*, space represents an interval of forty minutes of continued hypotension; *3*, 0.2 cc. of angiotonin administered after seventy-eight minutes of sustained hypotension; *4*, intravenous infusion started; *C*, space represents an interval of twenty-three minutes during which infusion continued; *5*, 200 cc. of blood had been infused in twenty-five minutes; *D*, space represents an interval of sixty-three minutes during which infusion continued; *6*, infusion completed, 595 cc. of blood administered in ninety-three minutes; *E*, space represents an interval of twenty-five minutes; *7*, 0.2 cc. of angiotonin administered twenty-eight minutes after infusion started.

the blood removed that was actually returned intravenously, if it had been given intra-arterially, would have raised the arterial pressure to nearly normal levels.

Comparison of the Efficacy of Intra-Arterial and Intravenous Infusions if Only One Half of the Blood Removed Was Returned.—In all of the preceding experiments in which the dogs recovered after intra-arterial infusion, 100 to 175 cc. of blood had been enough to raise the arterial pressure to at least 60 mm. of mercury; therefore it seemed likely that dogs could be saved if only a part of the blood that

had been removed was returned. In preliminary trials, the restoration of 19, 25 and 33 per cent was not sufficient to cause survival but infusion of 50 per cent resulted in recovery. In the dogs receiving less than 50 per cent, death occurred within four hours after the infusion had been completed.

Half of the blood withdrawn was returned intra-arterially in 20 experiments and intravenously in another 20 (tables 6 and 7). Arterial pressure in the first group of animals was quickly elevated above the initial infusion pressure in all experiments except 1 (experiment 43, table 7). In this experiment there was no response, and the dog died soon after infusion was stopped. In 4 experiments (nos. 44, 45, 46 and 47, tables 6 and 7) arterial pressure after infusion was more than 85 mm. of mercury. It began to decline within one or two hours, and the dogs were dead twelve hours later. Postmortem examinations revealed hemorrhages in the spleen, liver and intestines. The intestine contained serosanguineous fluid and the mucosa was hemorrhagic.

The remaining 15 dogs treated by the intra-arterial method recovered. Bloody diarrhea similar to that observed in the dogs in which sustained hypotension was not treated appeared in some dogs after arterial pressure had been restored by returning one half of the blood.

Of the 20 dogs treated by the intravenous method, only 6 recovered and 14 died within the first twelve hours after treatment. The arterial pressure failed to increase in only 1 dog, and this animal died (no. 58, tables 6 and 7). In the remaining 19 dogs it rose gradually during the infusion. It was as high as, and sometimes higher than, it was at the end of the intra-arterial infusion of the same proportion of blood. However, in 13 dogs the pressure was not maintained; 6 were dead within six hours, and the remaining 7 died within twelve hours. The postmortem observations were the same as those described for the dogs which died after intra-arterial infusion.

The Effect of Sustained Hypotension and Treatment by Infusion on the Pressor Response to Angiotonin and Epinephrine.—The use of epinephrine and angiotonin in tests of the effects on the vascular system of hypotension and of the efficacy of treatment proved to be of value on two scores: First, objective evidence was provided that vascular reactivity to angiotonin and epinephrine had been uniformly depressed by hypotension. Second, when the response to these substances was not restored by treatment all of the dogs died in twelve hours despite the fact that arterial pressure was at first elevated to normal levels by the treatment. However, restoration of response did not insure survival.

With respect to angiotonin, hypotension almost abolished the pressor response in 23 dogs and in 16 of these restoration of arterial pressure, regardless of the method of administering the blood, resulted in a return to responsiveness. Two of these dogs died, and 14 recovered. Of the 7 in which responsiveness did not return, all died within twelve hours. To save space, these results are not included in the tables.

The rate of loss of responsiveness to angiotonin and epinephrine was compared in 4 dogs (nos. 28, 29, 43 and 54, tables 6 and 7). Parallelism was definite in each.

The average response to epinephrine was reduced by the period of hypotension from 37 to 5 mm. of mercury in 37 dogs. Seventeen of these dogs died within twelve hours after infusion, 1 of them before the test could be made. A pressor response to epinephrine was obtained in 14, and was absent in 2 of them after treatment. Twenty dogs recovered and they all responded to epinephrine after treatment.

The Intra-Arterial Infusion of Plasma in Human Beings.—Three patients who were in profound post-traumatic shock received intra-arterial infusions of plasma. Before the infusion was started the blood pressure was less than 50 mm. of mercury in all of them. The arterial pulse was not palpable in any of the peripheral arteries. The radial artery was dissected out at the wrist and a 14 gage needle inserted. The needle was placed in the artery so that the infusion would flow toward the heart.

The inflow of plasma was very rapid for a few minutes, and the arterial pressure rose quickly, so that within five or ten minutes the blood pressure was 75 systolic and 40 diastolic in the first patient, 80 systolic and 35 diastolic in the second and 96 systolic and 40 diastolic in the third. This rapid rise in arterial pressure was associated with infusion of several hundred cubic centimeters of plasma. Arterial pulse was now palpable in the radial artery in the opposite arm.

Meanwhile, the heart rate decreased 10 to 20 beats per minute and the force of the apex beat definitely increased. As arterial pressure continued to rise, the systolic pressure exceeded the infusion pressure and inflow of plasma became intermittent. When the diastolic pressure exceeded the infusion pressure, the infusion ceased. At times the blood pressure forced blood out into the tubing and arterial pulsation could be seen in it.

All of the patients were treated surgically for their injuries. During the operations the arterial pressure was maintained by intermittent intra-arterial infusion. Five hundred to 1,000 cc. of whole blood in addition to plasma was administered to each patient. The blood pressure of all patients was at least 100 mm. of mercury systolic and 50 diastolic when the operations were completed. After five or six hours of intermittent infusion the needle was removed and the artery ligated.

One patient died of shock twenty-four hours later. The blood pressure in this patient could not be maintained by intravenous infusion after the arterial infusion had been stopped. The second patient died four days later, probably from a cause not directly related to shock. The third patient recovered.

In the patient who lived four days and in the one who recovered, an area of sloughing appeared on the flexor surface of the forearm which had been used for the intra-arterial infusion. This area paralleled the distribution of branches of the radial artery. The patient who recovered showed no other ill effect from ligation of the radial artery.

COMMENT

The apparatus and method of bleeding used in these experiments offer a convenient and practical means of producing severe, sustained hypotension with a minimal danger of bacterial contamination. Another important advantage of the technic is that excess citrate solution is not used. The dogs therefore will not at any time receive blood containing more citrate than is necessary to prevent clotting.

The narrow margin of safety at the low arterial pressure of 30 mm. of mercury necessitated arrangement of the apparatus so that blood could be returned quickly if arterial pressure began to fall below this level. After some practice, we were able to maintain it within ± 8 mm. of mercury of the desired level.

Courage is sometimes needed to withdraw enough blood so that too much time does not elapse before the level of 30 mm. of mercury is reached. In most experiments it was attained within forty minutes of the first hemorrhage and sustained for forty minutes or more.

Methods have not so far been devised for determining the severity of the effects of hypotension on the vascular system. For this reason we have used as a means of estimating these effects Page's [1] observation that hemorrhage reduces or abolishes the response to angiotonin and that restoration of normal blood pressure does not necessarily restore responsiveness. Epinephrine hydrochloride was also found to be of use and seemed to parallel the action of angiotonin, though it is perhaps not as sensitive. In most dogs the period of hypotension required to abolish the response was from forty to sixty minutes, but in a few more time was necessary. It is possible that angiotonin and epinephrine and other substances which test vascular reactivity may be used as a means of standardizing the effects of hemorrhagic hypotension.

One fact stands out clearly. When the response to angiotonin or epinephrine hydrochloride is not restored after treatment the chance of survival is very poor. However, the return of responsiveness does not guarantee survival.

The intra-arterial method has been used by Davis, Jermstad and Choisser [2] for administration of hypertonic solution of sodium chloride in the treatment of shock, but Kendrick and Wakim [3] suggest that the solution may be deleterious. The pressor action observed was nervous in origin, since it disappeared on section of the spinal cord. Kendrick [4] later found that 5 per cent solution of dextrose was more effective in experimental shock due to intestinal trauma when given by vein than by artery. These experiments, therefore, do not suggest that the intra-arterial method has any value as a mode for administering dextrose or hypertonic solution of sodium chloride. Administration of blood or plasma has apparently not been tried.[5]

The intra-arterial method for infusion of blood was first compared with the intravenous in a group of dogs in which all of the blood removed was returned. The results indicate the former has the one advantage over the latter of more rapid elevation of arterial pressure. The speed with which elevation is brought about probably enabled us to save 2 dogs of a group of 8. During a later experiment of the same nature the 2 survivors died after intravenous infusions.

Preliminary experiments conducted to ascertain roughly the minimum amount of blood it was necessary to return to insure survival showed that even by the intra-arterial route 25 to 35 per cent produced only a temporary rise in pressure. If 50 per cent was returned, 15 of 20 dogs recovered, and infusion of only 100 to 175 cc. of blood elevated the blood pressure to about 70 mm. of mercury in all but 1 of the animals. In contrast, only 6 of 20 of the animals treated intravenously with the same proportion of blood survived. It is interesting that the intravenous infusion raised the arterial pressure of 19 of the 20 dogs to 70 mm. of mercury or higher but in 13 of these the rise was only temporary and death occurred within twelve hours.

Measurement of intrathoracic venous pressure was used as a guide to the rate of administration of the infusions. If it rose more than 5 cm. of water the rate was reduced. It was found that if in the face of this warning the infusion was continued acute circulatory failure often caused death. Whether or not a rise in venous pressure would occur after the infusion was not predictable. Some animals were able to cope with large amounts of blood given rapidly

2. Davis, H. A.; Jermstad, R. J., and Choisser, R. M.: Proc. Soc. Exper. Biol. & Med. **37**:144, 1937.

3. Kendrick, D. B., and Wakim, K. G.: Proc. Soc. Exper. Biol. & Med. **40**:114, 1939.

4. Kendrick, D. B.: Surgery **6**:520, 1939.

5. After this paper was in press we found a publication by I. A. Birillo in a Russian journal (Khirurgiya **8**:3, 1939) in which the intra-arterial method was employed with success.

without an alarming rise, and others were not. In general, when a large volume of blood flowed in rapidly under a pressure of 50 mm. of mercury and no corresponding immediate rise in arterial pressure occurred, circulatory failure with rise in venous pressure might be anticipated.

To ascertain the practicality of administering blood or plasma intra-arterially to human beings, 3 patients in profound traumatic shock were treated by this method. The radial artery proved easy to cannulate, but the femoral artery is often easier. The difficulty with the latter is keeping the needle in place if the patient is not cooperative. From our experience with these patients we believe that the method is practical and might be used when insufficient plasma is available or arterial pressure is excessively low. In the latter circumstance it would seem wise to measure venous pressure and be guided by it for the rate of administration of blood or plasma.

SUMMARY

A method for producing hemorrhagic shock is described which produces severe sustained hypotension without increase of bacterial contamination or the use of excessive amounts of anticoagulants. Spontaneous recovery does not occur. An apparatus is described for return of the blood removed through an artery under controlled pressure.

The severity of the effects of the hypotension on the vascular system was ascertained by the pressor response to angiotonin or epinephrine. If the response is not restored after treatment the chance of survival is poor, but the return of responsiveness does not insure survival.

When all of the blood removed is returned by the intra-arterial route under a pressure of 50 mm. of mercury the systemic arterial pressure rises rapidly and recovery occurs. The same amount of blood given intravenously usually causes recovery, but not quite so certainly as blood given into the artery.

Readministration of only 50 per cent of the blood by vein resulted in recovery of 30 per cent of the dogs, while the same amount given intra-arterially resulted in recovery of 75 per cent.

When blood is given intra-arterially to animals with severe hypotension two precautions should be observed: 1. The pressure should not be greater than 50 mm. of mercury, and it should be elevated stepwise. 2. The rate of administration of the fusion should be guided by the venous pressure.

Intra-arterial infusions have been given 3 patients in severe shock to demonstrate the practicality of the procedure.

It is suggested that the method may have value when the amount of plasma or blood available is insufficient or when the arterial pressure is excessively low.

Mr. Clifford Wilson assisted in the experiments.

960 Locke Street.

BILATERAL CARCINOMA OF THE ADRENAL CORTEX WITH METASTASIS TO THE ILIAC BONE

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Carcinoma of the adrenal cortex is rare, and instances of simultaneous involvement of both adrenals are still rarer. In addition, metastases of such tumors to bone have been reported infrequently. These facts have led us to believe that a report of the following case may be of value:

REPORT OF A CASE

W. D., a white man 57 years of age, entered St. Luke's Hospital on March 17, 1939. His chief complaint was pain of six months' duration in the region of the right hip. He fell in September 1938 and bruised the right hip and since that time had had pain on movement, relieved at first by rest. The pain at times radiated along the right sciatic nerve. A punch biopsy was carried out at another hospital, but the report stated only that the patient had a "tumor." He had lost 19 pounds (8.6 Kg.). Just prior to his admission to the hospital there had been constant sciatic pain. There was localized tenderness in the inguinal region, so that the patient described it as "feeling like a boil." He admitted slight addiction to alcohol and said that he smoked two packages of cigarets a day. His usual weight had been 138 pounds (62.6 Kg.), and on admission it was 120 pounds (54.4 Kg.). The rest of his history was essentially noncontributory.

Physical examination: The patient was a well developed but undernourished middle-aged white man lying comfortably in bed. His breath had a strong alcoholic odor. The skin and mucous membranes were normal. The head showed no deformity and there were no areas of tenderness. The pupils were equal and reacted to light and in accommodation. Hearing was acute, and there was no discharge from the ears. There was no nasal obstruction or discharge. The mouth was edentulous; the tongue was clean and moist. Examination of the neck did not reveal any swelling or tenderness. The pharynx was clear. The chest was barrel shaped, and there was considerable limitation of expansion. The posterior portion of the chest on the right side was somewhat more prominent than on the left. The respiratory murmur was virtually absent over the entire posterior portion of the chest and noticeably diminished over the anterior portion. There were no rales. Fremitus and resonance were normal.

The heart was not enlarged; the peripheral vessels were somewhat thickened and the sounds distant. The rate and rhythm of the heart beat were normal. The blood pressure was 120 systolic and 74 diastolic.

Palpation of the abdomen revealed neither tenderness nor masses. The liver was at the costal border. The spleen was not felt. There were no scars. The genitalia were essentially normal.

There was definite evidence of pain in the region of the right hip when weight was borne on the leg. Motion in the hips was limited, and both great trochanters were prominent. There was a mass involving the right iliac crest and the right anterior superior iliac spine. The tumor was both deeply and superficially attached. The entire area involved was indurated but not particularly tender and measured roughly 8 to 10 cm. in diameter.

The right knee jerk was questionably present. The left knee jerk and both ankle jerks could not be elicited.

There was no deformity of the spine and no tenderness. Motion in the spine was normal.

The urine was normal and its specific gravity was 1.024.

The blood count revealed a hemoglobin content of 95 per cent. There were 4,250,000 red cells and 12,000 white cells per cubic millimeter of blood. Sixty-four per cent of the white cells were polymorphonuclear leukocytes, 34 per cent lymphocytes and 2 per cent basophils.

From the Orthopedic and Pathologic Services of St. Luke's Hospital.

The Kline test for syphilis gave negative results.

Roentgen examination on March 19, 1939 revealed a destructive process involving the right ilium. It extended from a point almost 2 cm. beyond the anterior superior spine downward to within 1 cm. of the acetabulum. The appearance suggested a tumor (fig. 1). Examination of the chest showed the heart, aorta and diaphragm to be normal. The pulmonary fields appeared clear (fig. 2).

Fig. 1.—Roentgenogram of the pelvis, showing a destructive lesion in the right iliac bone.

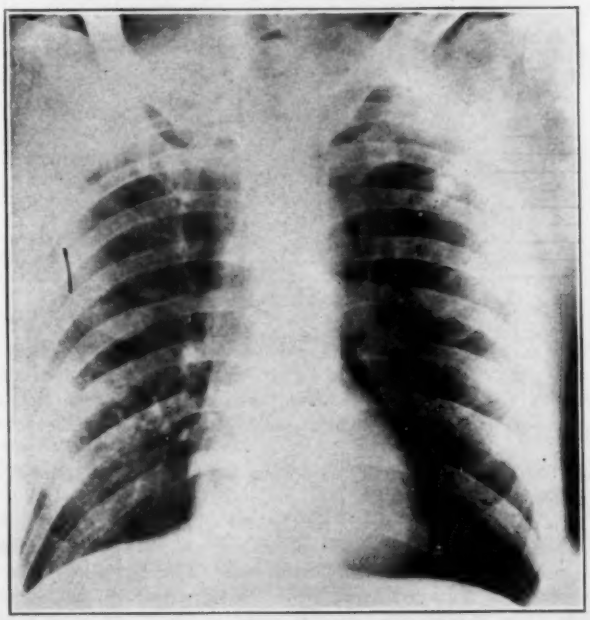

Fig. 2.—Roentgenogram of the chest, showing no evidence of metastatic carcinoma.

A preoperative diagnosis of neoplastic disease was made, and an exploration or biopsy of the tumor was proposed to determine the proper treatment.

The operation was performed on March 27, 1939. With the patient under cyclopropane anesthesia a 4 inch (10 cm.) incision was made over the iliac crest and deepened to expose the tumor. Sections were removed, and the wound was closed with interrupted silk sutures. The time of operation was twenty-five minutes.

At the site of the right iliac crest and below there was found a large mass of tissue which appeared necrotic. The iliac crest was replaced by cartilaginous-appearing yellowish tissue. After examining frozen sections the pathologist reported that the tumor was probably sarcoma. Because of the wide extent of involvement of the ilium and the soft tissues, no attempt was made to remove more of the mass of tissue than was necessary to identify its malignant nature.

Two hours after operation the patient had a rapid pulse, was sweating and had not reacted from the anesthesia. One hour later respirations were noted to be rapid, and the pulse was of poor quality. The extremities were cold. There was no bleeding from the wound. He was given an infusion of 1,500 cc. of 5 per cent solution of dextrose in physiologic solution of sodium chloride and blankets were applied and shock blocks placed under the foot of his bed. Three hours later his condition had improved but he had not become conscious. The following day his temperature rose from 101 F. at 8 a. m. to 105 F. at 12 p. m.

A medical consultant saw him at 11 a. m. and suggested the possibility of a cerebral accident and ordered an intravenous infusion of 100 cc. of 25 per cent solution of dextrose in physiologic solution of sodium chloride, which was given at 2 p. m. A roentgenogram made with portable apparatus showed no evidence of pneumonia. During the day he was given ⅙ grain (0.01 Gm.) of morphine sulfate for restlessness. His pulse varied in rate between 120 and 130 and was of poor quality. His respirations rose during the day from 30 to 48 per minute. His last recorded temperature, at 4 a. m. on the second postoperative day, was 105.8 F. He died at 6:45 a. m., never having regained consciousness or rallied from shock after a simple operation.

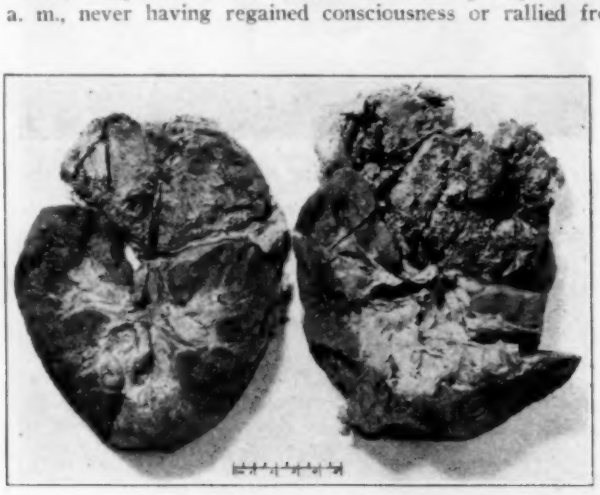

Fig. 3.—Photograph of adrenal tumors and kidneys.

Autopsy.—The body was that of an emaciated white man 57 years of age. Over the right superior iliac crest was an incision 11 cm. in length, made for removal of the biopsy specimen. Palpation in this region revealed loss of bone from the iliac crest and the region of the anterior superior iliac spine. The superficial cervical, axillary and inguinal lymph nodes were not enlarged.

The brain showed no lesions except moderate arteriosclerotic changes in the cerebral vessels. The pituitary appeared normal.

The right lung was collapsed and fixed to the wall of the chest by numerous fairly firm fibrous adhesions. There was no free fluid in either pleural cavity. The right lung was atelectatic, with occasional areas of bronchopneumonia. The left lung was relatively normal.

The entire gastrointestinal tract was free from gross pathologic changes.

The liver was free from tumor, the surface appearing generally pale with some chronic congestion. The gallbladder was normal, and the ducts were patent. The pancreas was normal in size and presented no gross lesions. The spleen weighed 175 Gm. and appeared normal.

The kidneys were normal in size; the capsules stripped with ease, and a fairly smooth surface was left. The corticomedullary markings were normal. In the right kidney immediately under the capsule and replacing the cortex was a small spherical encapsulated tumor, 1.5 cm. in diameter, pale gray, firm and of homogeneous structure. The ureters and bladder presented no pathologic changes.

The bodies of the vertebrae showed no invasion by the tumor.

The lymph nodes along the course of the aorta and iliac vessels were not enlarged.

The adrenals were both practically destroyed and had been replaced by thinly encapsulated tumor masses, the right being 7 by 7 by 5 cm. and the left slightly smaller (fig. 3). They were entirely distinct from the kidneys and adjacent fat. The tumors were discrete and rather soft and on section were extremely friable. They were composed of pale grayish white tissue without definite fibrous structure or noticeable vascularity. The normal adrenal markings were not recognizable, and in cross sections only a few minute areas of orange-pigmented cortex could be detected. No medulla was found.

In the anterior part of the right iliac bone the hemorrhagic cavity formed by the removal of tissue for biopsy was found filled with blood clots. The adjacent bone was soft, friable and obviously infiltrated by tumor over an area 4 by 6 cm. Outside the bone large, soft lobulated masses of tumor extended down through the gluteus medius muscle. Here the growth was white, opaque and homogeneous except for a few hemorrhagic areas (fig. 4).

Anatomic Diagnosis.—Bilateral adrenal carcinoma; metastasis to right iliac bone and adjacent muscles; adenoma of right kidney; bronchopneumonia.

Microscopic Examination.—No normal adrenal tissue was found, both cortex and medulla being replaced by masses of large flat cells, often detached and mostly without a well preserved cell membrane. Many presented a ragged or crushed appearance. Elsewhere they seemed to be growing in sheets, very loosely joined together. The cell bodies were in general somewhat polygonal with short blunt processes, but some were narrow and elongated (figs. 5 and 6). The cytoplasm was slightly hydropic or homogeneous with the eosin stain. There were no collagenous fibrils extending from or between the cells. The yellowish streaks noted in the gross showed intracellular and extracellular orange-colored granular pigment, possibly the remnants of the adrenal cortical cells. Stains for fat revealed no lipid material.

Fig. 4.—Photograph of the ilium, part of the ischium and the pelvic bone, showing the site of metastasis involving the iliac crest and the body of the pelvic bone.

The nuclei were often very large but showed wide variations in size and shape. There were some oval cells and other lobulated or giant forms. Nearly all were vesicular with a prominent nucleolus. Mitoses were infrequent, but the largest cells usually contained masses of deeply stained chromatin or exhibited bizarre degeneration forms.

There was no special alveolar or perivascular arrangement, no papillary structure and practically no interstitial connective tissue. Blood vessels were infrequent, only a few small venous channels being intact. There were some fresh hemorrhage and many large areas of necrosis. Tumor emboli were present in the blood vessels of the capsule. There was no resemblance to cells of the outer layers of adrenal cortex, but the structure of the inner reticular zone was still preserved, there being a loosely whorled or distorted stellate pattern in which the cells appeared to be attached at one pole.

It would be impossible to state in which adrenal the tumor first arose, but since the tumor on the right side was somewhat the larger, it was perhaps older. Bilateral tumors of the adrenals, like those of other paired organs, are usually regarded as independent growths arising simultaneously under the same stimulus. Bilateral metastases do of course occur,

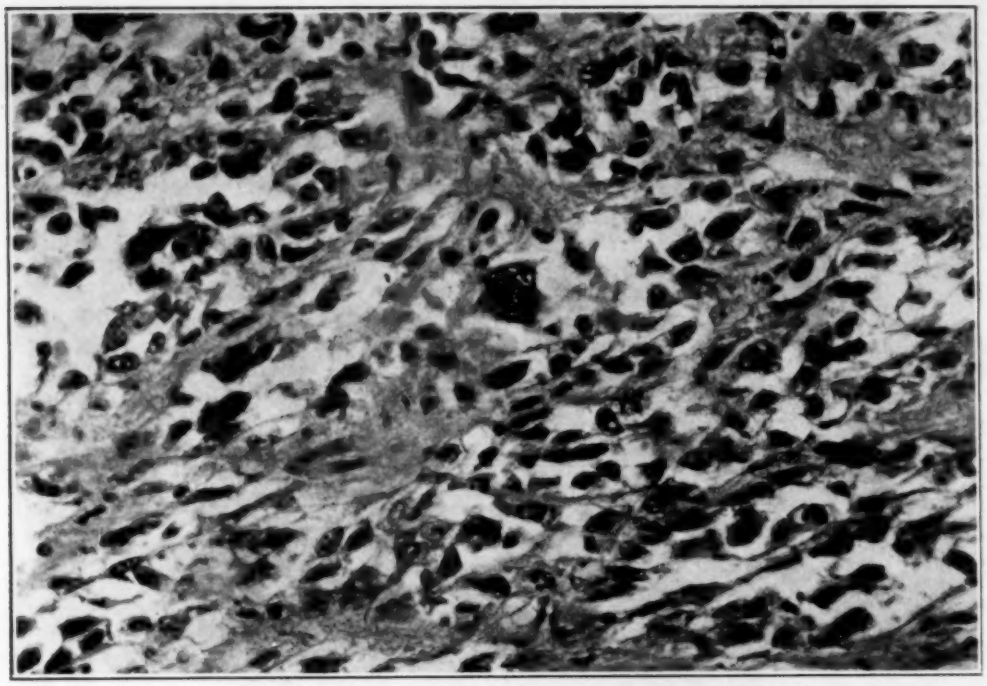

Fig. 5.—Photomicrograph of an adrenal carcinoma, showing loosely attached, elongated cells with reticulated pattern. The nuclei are generally large but show wide variations in both size and shape (× 300).

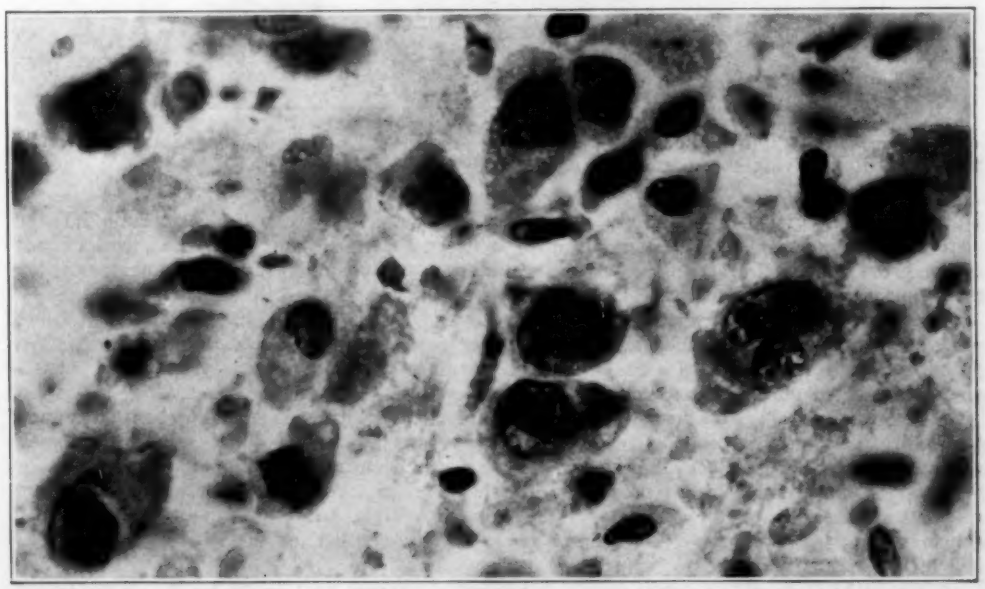

Fig. 6.—High power photomicrograph of an adrenal carcinoma, showing granular and vacuolated cells and large irregular nuclei (× 700).

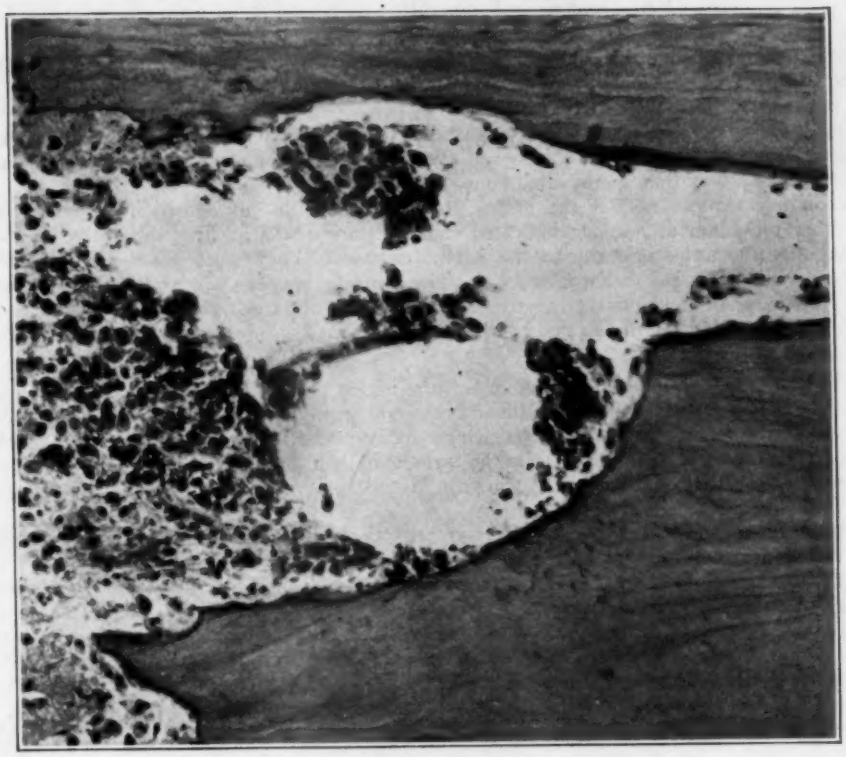

Fig. 7.—Photomicrograph of bone from the ilium, showing metastatic tumor with necrosis of the bone (× 200).

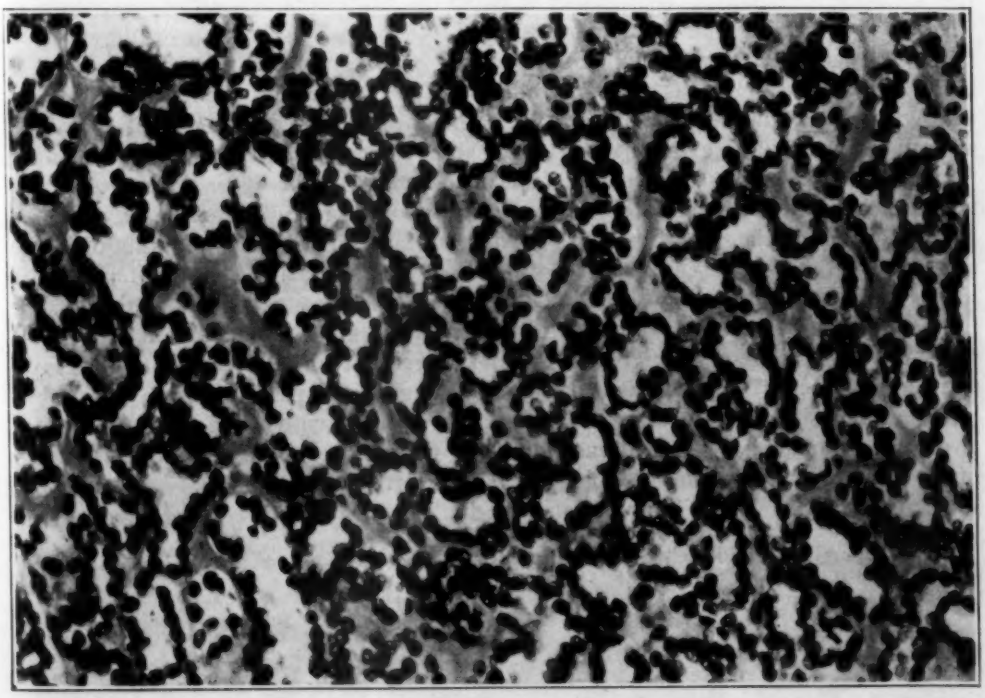

Fig. 8.—Adenoma of the right kidney. Small compact epithelial cells line the tubules (× 300).

usually when the retroperitoneal lymphatics are widely involved, as in the late stage of renal or pancreatic carcinoma, or they may even originate from the hilus of the lungs when bronchogenic tumors are present.

It must be noted that in this case metastases to the lymph nodes, involvement of the fatty or fascial tissue between the two adrenals and pulmonary metastases were absent. The only secondary tumor was that in the iliac bone.

Microscopic examination of the biopsy tissue restudied in juxtaposition with the material taken from the ilium at autopsy indicated that the large cells at first suggestive of sarcoma were actually the same as those of the adrenal tumors. They were not derived from osteoblasts, nor did they have characteristics of any myeloid cells. They invaded the marrow spaces, replacing fat and connective tissue with masses of large, often detached cells, poorly vascularized and showing much necrosis. Osteoblasts had disappeared (fig. 7), and the bone was undergoing necrosis.

Sections of the small cortical tumor of the right kidney showed it to be an adenoma unrelated to the adrenal neoplasm. It had a definite papillary structure and was composed of compact, deeply stained epithelial cells which formed small glandular structures resembling renal tubules (fig. 8). The cells were uniform and their arrangement regular. The size of this tumor was rather unusual, since growths of this type are seldom more than a few millimeters in diameter.

Sections of the pituitary revealed normal cells, and no significant changes were found in either the anterior or the posterior lobe.

Microscopic examination of the other organs did not disclose metastases or other significant lesions. Early bronchopneumonia was present in portions of the lung.

The cortical cells of the adrenal, while mesodermal in derivation, take on in the course of their development the form and functions of specialized epithelium; hence the tumors derived from them are usually called carcinoma.

The final diagnosis was bilateral carcinoma of the adrenal cortex, reticular type, with metastasis to the right iliac bone and the gluteal muscles and adenoma of the right kidney.

COMMENT

Interest in this group of neoplasms was awakened in 1896 by the publication in the *Edinburgh Hospital Reports* of a paper by Affleck and Leith [1] describing a tumor which occurred in a man 46 years old suffering from weakness and stiffness of the legs and back and complaining of loss of weight for a year, with pain for three months. There was no pigmentation of the skin. At autopsy a soft, pale yellowish white tumor was found in the right adrenal. The left adrenal contained a similar but smaller growth, and there were widespread metastases. The next year Kelynack [2] reviewed 26 cases of cortical tumors of the adrenal collected from the earlier literature, while only a year later Rolleston and Marks [3] published a survey of all of the previously reported cases and attempted to distinguish the adenomas from the carcinomas. Only 14 were thought by these authors to be unmistakable carcinomas. There was, however, at this time no realization of the frequency of metastases of bronchial tumors to the adrenal, so that one may question whether some of these nonpigmented tumors were not metastases. In 1904 Hartmann and Lecène [4] again reviewed the subject, giving special attention to a tabulation of the sites of metastases in all of the patients who came to autopsy, but after this comparatively little was added to the subject until about 1930, when important advances in endocrinology brought forth case reports of patients who showed the remarkable biologic effects due to hormones secreted by adrenal

1. Affleck, J. O., and Leith, R. F. C.: Clinical Observations on a Case of Sarcoma of the Suprarenal Capsules, Edinburgh Hosp. Rep. **4**:278, 1896.

2. Kelynack, T. N.: Adrenal Growths, M. Chron. **7**:401, 1897.

3. Rolleston, H. D., and Marks, H. W. J.: Primary Malignant Disease of the Suprarenal Bodies, Am. J. M. Sc. **116**:383, 1898.

4. Hartmann, H., and Lecène, P.: Les tumeurs de la capsule surrénale, in Hartmann, H.: Travaux de chirurgie anatomo-clinique, Paris, G. Steinheil, 1904, series 2, pp. 14-43.

tumors. Unfortunately, even yet few of the cases have been studied both from the biologic and from the morphologic point of view.

Especially noteworthy for the clinicopathologic data are the recent paper of Lescher and Robb-Smith [5] and that of Cahill, Loeb, Kurzrok, Stout and Smith.[6] The latter includes reports on 4 patients who came to operation and the autopsy record of a patient seen in the terminal stage of the disease. Of the surgical patients 1 was living and well at the time of the report, about a year after operation; 2 died of metastases ten and twenty-seven months after operation, and 1 succumbed thirty-six hours after operation. This paper contains a full discussion of the clinical observations in these cases and an excellent review of the subject.

We feel that it is still doubtful whether the adenomas can always be morphologically distinguished from carcinomas. In the adrenals, as in other endocrine glands, especially the thyroid, metastasizing tumors arise whose structure is still that of a benign growth or even of hyperplasia, without definite indication of a neoplasm. Some of these tumors, as in the remarkable cases of Calder and Porro,[7] Ashe,[8] Feinblatt [9] and Lukens, Flippin and Thigpen,[10] have so interfered with metabolism as to cause death. Hence we include here some tumors described as adenomas since metastases were not present, even though a number of them proved rapidly fatal. Other tumors appear to have been cured by operation, and the patients were still well at the time of the report.

Our review of 49 cases from the literature shows that 18 of the tumors occurred in men, 23 in women and 8 in children under 14. Of the 23 women, 12 were in the fourth decade. Six of the 17 men whose age was given, the largest number in any one age group, were in the fifth decade, slightly older than most of the women. Tumors in girls aged 23 months and 3, 7½, 9, 11 and 13 years have been described by Walters,[11] Ashe,[8] Little,[12] Lawrence [13] and Babonneix, Delarue, Golé and Jourdan.[14] In boys under 14 these tumors are even more rare. Player and Lisser [15] reported one in a boy 4 years of age who was well twenty months after operation. The patient of Fordyce and Evans [16] died twelve hours after operation and was found at autopsy to have metastases to the liver and the brain.

5. Lescher, F. G., and Robb-Smith, A. H. T.: A Comparison of the Pituitary Basophilic Syndrome and the Adrenal Corticogenital Syndrome, Quart. J. Med. **4**:23, 1935.

6. Cahill, G. F.; Loeb, R. F.; Kurzrok, R.; Stout, A. P., and Smith, F. M.: Adrenal Cortical Tumors, Surg., Gynec. & Obst. **62**:287, 1936.

7. Calder, R. M., and Porro, F. W.: Adenoma of Adrenal Cortex Simulating Pituitary Basophilism (Cushing's Syndrome), Bull. Johns Hopkins Hosp. **57**:99, 1935.

8. Ashe, J. R.: Adenoma of Suprarenal Cortex, Tr. M. Soc. North Carolina **81**:258, 1934.

9. Feinblatt, H. M.: Carcinoma of Cortex of Suprarenal Gland with Virilism, Arch. Int. Med. **38**:469 (Oct.) 1926.

10. Lukens, F. D. W.; Flippin, H. F., and Thigpen, F. M.: Adrenal Cortical Tumor with Absence of Opposite Adrenal: Report of a Case with Operation and Autopsy, Am. J. M. Sc. **193**:812, 1937.

11. Walters, W., and Kepler, E. J.: Adrenal Cortical Tumors and Their Treatment, Ann. Surg. **107**:881, 1938.

12. Little, A. A., Jr.: Carcinoma of the Adrenal Cortex, J. Pediat. **9**:62, 1936.

13. Lawrence, C. H.: Adrenal Cortical Tumor: A Report of Four Cases, Ann. Int. Med. **11**:936, 1937.

14. Babonneix, L.; Delarue; Golé, L., and Jourdan (Mme.): Epithélioma cortico-surrénal chez une jeune fille de treize ans et demi, Bull. Soc. de pédiat. de Paris **33**:258, 1935.

15. Player, L. P., and Lisser, H.: Adrenal Sexual Precocity Caused by Tumors of Adrenal Cortex, Urol. & Cutan. Rev. **37**:758, 1933.

16. Fordyce, A. D., and Evans, W. H.: Virilism with Report of Two Cases: Pathological Reports, Quart. J. Med. **22**:557, 1929.

Carcinoma of the adrenal cortex is occasionally bilateral, but some of the reported cases were not instances of primary carcinoma. The growth in Rosenstein's [17] case, for example, was apparently some type of sarcoma.

The tumor described by Affleck and Leith [1] was also bilateral, but there was such extensive invasion of the retroperitoneal tissues that the two masses nearly met in the midline. In the case of Rimbaud [18] the right adrenal was grossly involved, and microscopic examination revealed that the left had also been invaded. Grynfeltt and Rimbaud,[19] Weinberg and Turquet [20] and Kimm and Wu [21] also described bilateral tumors. The last-named authors observed widespread metastases.

Among the 49 cases, therefore, we have found only 5 in which the tumors were bilateral, and in 4 of these the growths may have been secondary. The case of Kimm and Wu [21] was the only one closely resembling that reported here.

In studies of solitary tumors the condition of the opposite adrenal has been the subject of considerable interest. Lukens' patient with a solitary adenoma of the right adrenal was found at autopsy to have no left adrenal. The same abnormality was found in Feinblatt's [9] patient with a carcinoma in the right adrenal. Grynfeltt and Rimbaud [19] described a tumor arising from the zona fasciculata of the left adrenal. It was only moderately enlarged, while the right adrenal was hypertrophied. More often, however, the opposite adrenal has shown atrophy, as in the cases of Calder and Porro [7] and Little [12] and the second case of Lawrence.[13]

In the 40 cases in which we are reasonably sure of the site of origin, 14 tumors have been primary on the right side and 26 on the left.

The symptoms are extremely variable, since the specific biologic effects of abnormal hormones may or may not be present. Fewer symptoms are usually present if the patient is a male. Ten of 18 adult male patients showed no sexual abnormalities, while only 3 of 23 females were without structural sexual alterations. Before puberty such alterations may be absent, as in Ashe's [8] case of a girl 3 years of age who had an adenoma of the cortex associated with hypertension and cyanosis but who did not show unusual secondary sexual development.

In women the syndrome closely resembles that of Cushing's pituitary basophilism in that there is a diminution of the female characteristics associated with the appearance of certain male ones. Amenorrhea, obesity or loss of weight and changes in the skin (usually acneform coarsening and increase in the oily secretion), accompanied with hypertrichosis and striae, are frequent. Polycythemia with dusky red or cyanotic face or extremities, hypertension and headache are often present. Masculinization is shown by hypertrophy of the clitoris and masculine growth and distribution of hair on the face, trunk and extremities. In some cases extreme changes have taken place in the general habitus. In the male the syndrome is usually less well defined than in the female. Simpson and Joll [22]

17. Rosenstein, S.: Sarcom der Nebennieren mit Metastasen in Nieren, Pancreas und rechtem Herzen, Virchows Arch. f. path. Anat. **84**:322, 1881.

18. Rimbaud, P.: Syndrome addisonien à évolution rapide. Epithélioma cortical des capsules surrénales, Bull. et mém. Soc. méd. d. hôp de Paris **49**:404, 1933.

19. Grynfeltt, E., and Rimbaud, P.: Adénome cortical des capsules surrénales. Bull. Assoc. franç. p. l'étude du cancer **21**:614, 1932.

20. Weinberg and Turquet: Cancer des deux capsules surrénales avec noyau métastatique du cervelet. Mort subite, Bull. et mém. Soc. anat. de Paris **72**:751, 1897.

21. Kimm, H. T., and Wu, S. D.: Bilateral Adrenal Cortical Carcinoma, Chinese M. J. **59**:195, 1941.

22. Simpson, S. L., and Joll, C. A.: Feminization in a Male Adult with Carcinoma of Adrenal Cortex, Endocrinology **22**:595, 1938.

discussed 6 cases of the condition in men, in all of whom female characteristics were noted. Hypertrophy of the breasts was the first symptom in 4 patients, and in 3 it was associated with atrophy of the testes, loss of libido and gain in weight.

With the continued growth of the tumors remarkable skeletal changes may occur. Osteoporosis, especially in the bones of the skull and trunk, is rather frequent, but overgrowth of these bones may also take place. Extreme deformities due to fractures and compression of the bodies of the vertebrae may be associated with only slight involvement of the long bones of the extremities. Lescher and Robb-Smith [5] found osteoporosis also in 9 of 14 cases of basophilic adenoma studied at autopsy. The affected bones of patients with carcinoma of the adrenal cortex show no extensive fibrosis or accumulation of granulation tissue, such as occurs with osteitis fibrosa cystica, but there is extensive irregular atrophy of all bony trabeculae and of the cortex with at times some minute cysts and some dense osteoid tissue. The condition of the bone marrow varies. In the case of Calder and Porro [7] it was largely fatty, although the patient had a dusky red skin, but in the case of Lescher and Robb-Smith,[5] whose patient had been conspicuously cyanotic, the bone marrow in the middle third of the femur showed erythropoietic hyperplasia.

In spite of the general decalcification and multiple fractures the calcium content of the blood may be little altered. For instance, in the patient of Calder and Porro [7] the calcium content of the blood was 10 mg. and the phosphorus content 2.6 mg. per hundred cubic centimeters. In Lukens' [10] patient the calcium content of the blood was 10.4 mg. and the phosphorus content 3.4 mg. per hundred cubic centimeters. The value for phosphatase activity was 32 units. The patient of Kimm and Wu [21] had widespread osteolytic changes and the calcium content of the blood was 5.9 mg. and the phosphorus content 4.7 mg. per hundred cubic centimeters.

Tests for sex hormones in patients with adrenal carcinoma were reported in 1934 by Frank,[23] who found excessive amounts of estrogenic substance in the urine. Cahill [6] did not find large amounts in the tests on his patients, but much work remains to be done in this field.

In diagnosis, the exclusion of pituitary disease with or without tumor offers the greatest difficulty. Gamna and Forconi [24] in a survey of 39 patients with Cushing's syndrome found that 14, or 35 per cent, had no pituitary disease and that of these 14, 5, or 12.5 per cent of the total number, had tumors of the adrenal cortex. Graef, Bunim and Rottino [25] reported a case of adrenal carcinoma with coexistent pituitary adenoma.

Lawrence [13] stated that changes in the voice are always produced by adrenal tumors but not by pituitary tumors. Calder and Porro [7] emphasized the fact that although hypertrophy of the genitalia is not present in pituitary basophilism, its absence does not establish the diagnosis.

The prognosis in this group of carcinomas of the adrenal cortex is obviously poor; since they metastasize readily by way of the blood stream and grow rapidly, the duration of life without operation is short. Operation, though the mortality rate is high, has been successful in several cases. Walters and Kepler [11] at the

23. Frank, R. T.: A Suggested Test for Cortical Adrenal Carcinoma, J. A. M. A. **109**:1121 (Oct. 2) 1937.

24. Gamna, C., and Forconi, A.: Sulla patogenesi della distrofia adiposo-genitale osteoporotica (Morbo di Cushing), Minerva med. **1**:201, 1936.

25. Graef, I.; Bunim, J. J., and Rottino, A.: Hirsutism, Hypertension and Obesity Associated with Carcinoma of the Adrenal Cortex, Arch. Int. Med. **57**:1083 (June) 1936.

Mayo Clinic removed 5 of 7 of these tumors. The other 2 were infiltrating and hence inoperable. Three of Cahill's 4 patients [6] also recovered from operation, and Lawrence,[13] Player and Lisser,[15] Neumann [26] and Holl [27] have also reported successful extirpations with survival after operation for variable periods. Of a total of 40 patients who underwent operation about 50 per cent died very shortly. Lukens [10] stated that most fatalities occur within the first forty-eight hours. Walters and Kepler [11] expressed the opinion that when active, well directed postoperative treatment with adrenal cortical extract, sodium chloride, sodium citrate and sodium bicarbonate and a low potassium diet is carried out the surgical risk is not too great. The outstanding symptoms of adrenal insufficiency appear within eight hours after operation and include rapid pulse, fall in blood pressure, drowsiness, hiccups, nausea and vomiting. Insomnia, anorexia, weakness, apathy and restlessness may follow. Weil and Browne [28] stated that the adrenal cortex hormone is excreted in increased amounts after operations which do not involve the adrenals and that increased quantities of it appear postoperatively in the urine, the maximum being reached by the third to the fifth day. It is easy to believe, then, that the margin of safety of the patient with seriously damaged or atrophied adrenals is very low.

Metastases, if one may judge from the somewhat meager clinical records and from the data obtained from 18 autopsies, are most frequent in the lungs, liver and lymph nodes. The adrenal veins and the vena cava have been found involved. Less frequent are metastases to the brain, kidney, heart, peritoneum and pancreas. In contrast to the hypernephromas of the kidney, which readily metastasize to bone, the carcinomas of the adrenal have only infrequently been found to do so. In 1 other case, that of Kimm and Wu,[21] metastases were present in the iliac bone, as in our case, as well as in the vertebrae, ribs and scapula. When roentgenograms are studied it should be noted that the frequency of widespread decalcification and crushing is greater than that of skeletal metastases.

SUMMARY

A case of bilateral carcinoma of the adrenal cortex with metastasis to the right iliac bone has been presented. This patient showed no sexual abnormalities, such as have sometimes been reported in other patients with similar lesions. The tumor was recognized as a malignant growth involving the ilium. The cause of the patient's complete collapse after an extremely simple operative procedure was unrecognized before death, although he presented the classic signs of insufficiency of the adrenal cortex. Fortunately this clinical failure could not by any stretch of the imagination have affected the eventual outcome.

115 East Sixty-First Street.

St. Luke's Hospital.

26. Neumann, H. O.: Nebennierenrinde und Geschlechtlichkeit, Arch. f. Gynäk. **160**:481, 1936.

27. Holl, G.: Zwei männliche Fälle von Nebennierenrindentumoren mit innersekretorischen Störungen, Deutsche Ztschr. f. Chir. **226**:277, 1930.

28. Weil, P., and Browne, J. S. L.: The Excretion of Cortin After Surgical Operation, Science **90**:445, 1939; A Cortin-like Action of Extracts of Human Urine, Am. J. Physiol. **126**: 652, 1939.

CONFINEMENT TO BED FOR ONLY TWENTY-FOUR HOURS AFTER OPERATION

A MEANS OF PREVENTING PULMONARY AND CIRCULATORY COMPLICATIONS AND OF SHORTENING THE PERIOD OF CONVALESCENCE

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DETROIT

As a result of getting patients out of bed on the first postoperative day and increasing their activity as tolerated (with respiratory exercises mentioned hereinafter), circulatory and pulmonary complications have been reduced to a minimum, intestinal function has been restored without enemas and the period of morbidity and disability has been diminished 50 per cent or more.

A previous publication [1] on this subject precipitated editorial comments in several leading medical journals.[2] These comments enable me to correct erroneous impressions surgeons inexperienced with early rising have had regarding it. In addition I am presenting another series of 464 consecutive surgical cases in which practically all the patients were subjected to early rising.

This article also brings to attention specific reflexes that initiate pathologic changes—changes that lead to complications—and presents evidence that early rising, with its modifying effect on these reflex reactions, should be instituted by the first postoperative day.

Members of the medical profession have often inquired: "What stimulated interest in twenty-four hour confinement to bed after surgical procedures; and is there scientific evidence to support the theory that limiting confinement to bed to twenty-four hours is a means of preventing pulmonary, circulatory and other complications?" This study presents the scientific evidence, and the following case history is a reply to the first query.

In 1938, Mr. R. H., aged 38, disregarded orders and left his bed frequently a few hours after an appendectomy. Improvement was rapid as a result of frequent ambulatory activity, and on the following day he insisted on leaving the hospital. I was unable to convince him of the "danger" of such a procedure, and he left at his own risk. On the second postoperative day he drove 30 miles to run errands in busy downtown Detroit; on the third and fourth postoperative days he worked in the garden; on the fifth day he drove 40 miles for his first medical inspection following the operation. He was in excellent condition. This unusually rapid convalescence aroused my interest.

Unaware that the principle of early rising had been previously applied by surgeons here and abroad, I was so stimulated by this incident that thereafter I saw that practically all patients were got out of bed on the first day after an appendectomy and were permitted to leave the hospital the same afternoon, if they so desired, provided distention, abdominal rigidity or some other contraindication was not present. After a long and most gratifying experience with early rising after appendectomy, I applied the principle in other fields of abdominal surgery, and finally began to employ the method with all surgical patients, including those with

1. Leithauser, D. J., and Bergo, H. L.: Early Rising and Ambulatory Activity After Operation: A Means of Preventing Complications, Arch. Surg. **42**:1086-1093 (June) 1941.

2. Early Rising After Operation, editorial, New England J. Med. **226**:576-577 (April 2) 1942. Early Rising and Ambulatory Activity After Operation, editorial, M. Times **69**:440-441 (Oct.) 1941. Early Rising After Operation, Current Comment, J. A. M. A. **117**:1710 (Nov. 15) 1941.

ruptured appendixes. In each field of surgery, every patient operated on since early rising was instituted, whether subjected to this treatment or not, is reported on in this article.

A REVIEW OF THE LITERATURE

Early rising following celiotomy was first practiced routinely by Ries [3] over forty years ago. He was enthusiastic about this advantageous method of postoperative care. Most of his patients, including those operated on for hernia, were out of bed on the second day. He emphasized that eventration was not more common than when prolonged confinement to bed was insisted on. Binders were not employed, but adhesive straps were applied to infected wounds. However, the practice did not gain support until the late twenties, and then only in foreign lands.

Twenty-nine of the foreign articles have been studied and condensed for this review. Two patients who died of embolism were reported by Cotte.[4] Both were out of bed on the third day; one died on the fifth day and the other on the eighth day. However, Cotte stated that death in the latter case may have been due to heart failure. Chalier [5] was an enthusiastic exponent of early rising but was bitterly opposed by Violet [6] and Villard.[7] The latter presented at a meeting 2 unpublished cases of fatal embolism following early rising reported to him by a colleague. Chalier [8] analyzed these 2 cases and intimated that since neither Villard nor his colleague had any experience with early rising, their opinions must be considered in that light. Chalier reported 150 cases in 1929 and 606 cases in 1932.[5] His patients were out of bed between the third and the fifth day. He found no report in the literature that the practice had been discontinued because of ill effects. Zillmer [9] in 1930 reported on 524 patients who were out of bed on the first postoperative day. In 1935 Charbonnier [10] reported on 112 patients out of bed between the third and the fifth day. In 1935 Gullotta [11] reported 498 cases; some of the patients were out of bed on the second day. Coniglio [12] reported 151 cases, Salishchev and Ayziks [13] 194, Florcken [14] 219 and Ricci [15] 180. Other exponents

3. Ries, E.: Some Radical Changes in After-Treatment of Celiotomy Cases, J. A. M. A. **33**:454-456 (Aug. 19) 1899.

4. Cotte, G.: Fatal Embolism on the Eighth Day in a Woman Who Rose Early, Lyon chir. **36**:441 (July-Aug.) 1939.

5. Chalier, A.: Early Rising After Abdominal Operations, Lyon chir. **26**:834-844 (Nov.-Dec.) 1929; Evaluation of Early Rising in Abdominal Surgery After Four Years, ibid. **30**:122 (Jan.-Feb.) 1933.

6. Violet, H.: On the Subject of Early Rising for Operated Patients, Avenir méd. **29**:247-250 (Sept.-Oct.) 1932.

7. Villard: Two Cases of Fatal Embolism During the Course of Early Rising After Operation, Lyon chir. **30**:606-608 (Sept.-Oct.) 1933.

8. Chalier, in discussion on Villard.[7]

9. Zillmer: Favorable Results of Getting Up Shortly After an Appendectomy, Veröffentl. a. d. Geb. d. Heeres-San.-Wes., 1930, no. 84, pp. 127-138.

10. Charbonnier, A.: Early Rising After Operation, with Report of One Hundred and Twelve Cases, Rev. méd. de la Suisse Rom. **55**:402-466 (June 25) 1935.

11. Gullotta, G.: Early Rising for Operated Patients, Minerva med. **26**:322-325 (March 10) 1935.

12. Coniglio, G.: Concerning the Early Rising of Operated Patients, Riv. san. siciliana **23**:120-122 (Jan. 15) 1935.

13. Salishchev, V. E., and Ayziks, I. G.: Active Postoperative Regime (Early Rising), Novy khir. arkhiv. **36**:260-277, 1936.

14. Florcken, H.: Getting Up Following Surgical Operations, München. med. Wchnschr. **83**:917 (June 5) 1936.

15. Ricci, G.: Concerning Immediate Rising of Patients Who Have Undergone Operation, An. de cir. **2**:175-207 (Aug.) 1936.

were Folliasson,[16] Polichetti,[17] Pierre Smith,[18] Daumerie,[19] Wichmann,[20] Vincent,[21] Wohlleben,[22] and P. Smith.[23] All were enthusiastic over the rapid recovery and freedom from complications following early rising. Ricard [24] had six years' experience with this method without a single case of embolism. Correa [25] permitted his patients to be out of bed twelve hours after operation, while Mermingas [26] permitted patients to leave the operating room ambulatory after appendectomy under local anesthesia. Harild [27] emphasized the relief from the "sickbed feeling" as significant. Mukhina [28] reported 527 appendectomies performed during the acute stage of appendicitis; over 50 per cent of his patients were out of bed on the first postoperative day. Kimbarovskiy [29] reduced the incidence of pulmonary complications from both gynecologic and gastric operations to approximately one tenth through early rising. He also conducted experimental studies of healing of wounds on dogs in the ambulatory state and dogs forced into a reclining position by means of plaster casts. He [30] concluded that in the restricted animal there was a delay in the formation of connective tissue as the result of venous stagnation and a sluggish solution of fibrin. Shaus, Pozhariskiy and Abrikosob [31] in general expressed agreement with these conclusions. Dell'Oro [32] reported 1,569 cases, and Campeanu [33] 3,197 cases without complications. Zava [34] stated that among 6,000 patients out of bed on the first postoperative day there was not a single case of embolism or eventration. No special technic was employed.

The enthusiasm expressed by these authors is impressive. They reported that in over 15,000 patients subjected to early rising only 4 fatal emboli developed and at least 1 of these was questionable.

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16. Folliasson, A.: Early Rising in Abdominal Surgery, Bull. et mém. Soc. nat. de chir. **59**:1121-1127 (July 15) 1933.

17. Polichetti, E.: Early Rising After Laparotomy, Gazz. d. osp. **54**:1337-1340 (Oct. 22) 1933.

18. Smith, P.: Early Rising in Abdominal Surgery, Paris méd. **2**:68-73 (July 21) 1934.

19. Daumerie, L.: Concerning Early Rising After Operation, Bruxelles-méd. **18**:534-547 (Feb. 20) 1938.

20. Wichmann, S. E.: Concerning the Significance of "Early Rising" in the Prophylaxis of Thrombosis and Embolism, Acta Soc. med. fenn. duodecim (Ser. B., fasc. 1-2, art. 2) **27**:1-11, 1939.

21. Vincent, G.: Early Rising in Abdominal Surgery, J. de méd. de Paris **56**:252-253 (Sept. 24) 1936.

22. Wohlleben, T.: Early Rising After Operations, Arch. f. klin. Chir. **189**:382-385, 1937.

23. Smith, P.: Early Rising in Abdominal and Pelvic Surgery, Union méd. du Canada **69**:921 (Sept.) 1940.

24. Ricard: Embolism and Early Rising, Lyon chir. **36**:448 (July-Aug.) 1939.

25. Correa, B.: Immediate or Early Rising: One Hundred and Thirty-Eight Cases, Rev. brasil. de med. e farm. **12**:3-11, 1936; Lyon chir. **34**:37-48 (Jan.-Feb.) 1937.

26. Mermingas, K.: Early Rising After Operation, Zentralbl. f. Chir. **50**:2424-2425 (Sept. 27) 1930.

27. Harild, S.: Should One Allow Early Getting Up After Laparotomies or Not? Chirurg. **12**:703-707 (Dec. 1) 1940.

28. Mukhina, M. V.: Early Rising After Appendectomy in Acute Period, Vestnik khir. **40**:231, 1935.

29. Kimbarovskiy, M. A., cited by Khromov.[43]

30. Kimbarovskiy, M. A.: Experimental Study on the Effect of Early Rising on Healing of Postoperative Wounds, Novy khir. arkhiv. **48**:116-121, 1940.

31. Shaus, Pozhariskiy and Abrikosob, cited by Kimbarovskiy.

32. Dell'Oro, B.: The Immediate or Early Ambulatory Therapy After Surgery (Especially Abdominal): Method, Technic and Practical Results in 1,596 Cases, Rev. méd. de Rosario **26**:29-49 (Jan.) 1936.

33. Campeanu, L., and Papp, M.: The Importance of Early Rising Following Laparotomy, Zentralbl. f. Chir. **27**:1573-1579 (July 3) 1937.

34. Zava, L.: The Advantages of Early Rising After Operations, Policlinico (sez. prat.) **47**:865-872 (May 20) 1940.

COMPARATIVE ANALYSIS OF PREVIOUS AND PRESENT SERIES

In a previous publication [1] observations on 383 consecutive appendectomies were reported (cases of rupture excluded), with an average period of confinement to bed of one and five-tenths days. Sixty-six other consecutive surgical procedures, with an average period of confinement to bed of one and nine-tenths days, were also included in the series. There were no pulmonary or circulatory complications and no ill effects from early rising.

The present series of 464 consecutive operations is a continuation of the aforementioned series and consists of 274 appendectomies and 190 other major surgical procedures. Of the patients subjected to appendectomy 39 had chronic and 225

TABLE 1.—*Average Number of Days of Confinement to Bed and to Hospital After Operation in 464 Cases (Present Series)*

Classification of Operations	Total Cases	Days	
		Bed	Hospital
Appendectomy			
Chronic appendicitis	39	1.00	2.59
Acute appendicitis	225	1.00	2.40
Ruptured appendix	10	1.00	9.40
Celiotomy (exploratory)	4	1.00	12.50
Cholecystectomy	25	1.08	7.40
Cholecystotomy	1	1.00	22.00
Choledochostomy	4 *	1.00	6.75
Duodenal diverticulum, removal of	1	1.00	7.00
Gastrectomy, deaths	2 **	1.00	25.00
Gastrectomy, recoveries	1	1.00	10.00
Gastroenterostomy	1	1.00	7.00
Herniorrhaphy, inguinal, indirect (5 bilateral)	34	1.00	6.91
Herniorrhaphy, inguinal, direct (1 bilateral)	8	1.00	7.13
Herniorrhaphy, femoral (1 bilateral)	3	1.00	13.67
Herniorrhaphy, incisional	5	1.00	7.20
Herniorrhaphy, umbilical	4	1.00	4.50
Intestinal adhesions, separation of	1	1.00	4.00
Intestinal resection (obstruction)	1	1.00	17.00
Mastectomy (radical 5, simple 2)	7	1.00	5.29
Pelvic operations (hysterectomy, salpingectomy, oophorectomy, etc.)	33	1.00	6.97
Pelvic operations, tubal pregnancy	5	1.00	5.20
Pelvic operations, with perineal operations	4	1.00	10.00
Perforated duodenal ulcer	1	1.00	9.00
Perineal operations (interposition, colporrhaphy, etc.)	10	1.00	8.40
Rectal operations	15	1.00	3.93
Renal operations (nephrectomy, lithotomy, etc.)	6	1.00	10.83
Operations on the colon (cancer)	6	1.00	13.00
Thyroidectomy	8	1.75	5.25
Total	464 ***	1.02	4.68

* = 1 death.

acute appendicitis, and in 10 the appendix had ruptured. The average period of confinement to bed after appendectomy was one day, and the average period of postoperative hospitalization for the patients with acute or chronic appendicitis was two and five-tenths days. Patients with ruptured appendixes remained in the hospital for an average of nine and four-tenths days. After other major surgical procedures the average period of confinement to bed was one day, and the average period of hospitalization was seven and three-tenths days.[35] (For a statistical analysis of the two series, see tables 1 and 2.)

All patients were subjected to early rising except 2. One had had a cholecystectomy in which technical difficulties were encountered. (This patient was out of bed

35. Excluding the two deaths (gastric operation).

on the third postoperative day, and recovery was uneventful.) For the other, see case 1. For lack of space, minor complications which had no bearing on either the surgical procedure or early rising are not reported in this article, while all other complications are mentioned in case reports. (By early rising I now mean that the patient is to be out of bed by the first postoperative day, and only in rare instances by the second.)

It was necessary to rehospitalize 3 patients shortly after dismissal from the hospital. One, who left the hospital on the second day after a simple appendectomy, suddenly became ill with abdominal pain, chills and fever on the seventh day, after

TABLE 2.—*Average Number of Days of Confinement to Bed and to Hospital After Operation in 900 Cases (Present and Previous Series)*

Classification of Operations	Total Cases	Days	
		Bed	Hospital
Appendectomy			
Chronic appendicitis	147	1.4	2.5
Acute appendicitis	487	1.2	2.3
Ruptured appendix	10	1.0	9.4
Celiotomy (exploratory)	7 *	1.0	9.9
Cholecystectomy	43	1.3	7.8
Cholecystotomy	3	1.7	24.7
Choledochostomy	4 *	1.0	6.8
Duodenal diverticulum, removal of	1	1.0	7.0
Gastrectomy, recoveries	3	1.3	10.7
Gastrectomy, deaths	2 **	1.0	25.0
Gastroenterostomy	3	1.3	8.7
Herniorrhaphy, inguinal, indirect (5 bilateral)	41	1.1	6.8
Herniorrhaphy, inguinal, direct (1 bilateral)	10	1.2	7.0
Herniorrhaphy, femoral (1 bilateral)	3	1.0	13.7
Herniorrhaphy, incisional	5	1.0	7.2
Herniorrhaphy, umbilical	4	1.0	4.5
Intestinal adhesions, separation of	3	1.0	7.7
Intestinal resection (obstruction)	1	1.0	17.0
Marsupialization of pancreatic cyst	1	5.0	30.0
Mastectomy (radical 5, simple 2)	7	1.0	5.3
Pelvic operations (hysterectomy, salpingectomy, oophorectomy, etc.)	49	1.4	7.4
Pelvic operations, tubal pregnancy	5	1.0	5.2
Pelvic operations, with perineal operations	4	1.0	10.0
Perforated duodenal ulcer	1	1.0	9.0
Perineal operations (interposition, colporrhaphy, etc.)	10	1.0	8.4
Prostatectomy	1	2.0	18.0
Rectal operations	15	1.0	3.9
Renal operations (nephrectomy, lithotomy, etc.)	7	1.4	10.6
Splenectomy	2	2.0	8.5
Operations on the colon (cancer)	6	1.0	13.0
Thyroidectomy	15	1.8	5.6
Total	900 ****	1.3	4.0

* = 1 death.

recovery appeared complete. Since the complication, a peritoneal infection, occurred so late, suspicion was placed on the catgut. However, the condition completely subsided without surgical intervention. The second patient had undergone removal of a ruptured appendix. The wound was treated with sulfanilamide applied intraperitoneally and was closed without drainage. The patient was out of bed on the first postoperative day, and ambulation was gradually instituted. On the seventh day the patient appeared well and was permitted to leave the hospital. A few days later a cul-de-sac abscess developed, and the patient was rehospitalized for drainage (five days). The usual daily out of bed exercises were employed; there were no sequelae. For the history of the third patient see case 7.

Only 4 infections of wounds occurred, 1 after appendectomy and 1 each after femoral, incisional and inguinal herniorrhaphy. The 2 infections following incisional and inguinal herniorrhaphy developed in wounds closed with nylon sutures. Drainage was prolonged, and both patients were later rehospitalized at another institution. My experience with nylon was not satisfactory, since granulomas not infrequently occurred as late as ten months after its use. The use of this suture material has been abandoned.

The rapid recovery of patients operated on for appendicitis with rupture may be attributed to control of the infection with sulfanilamide applied intraperitoneally, to closing the abdomen without drainage and to early rising to avoid further complications. A small extraperitoneal drain was always employed.

There were 3 deaths in this series. One occurred before early rising was instituted.

CASE 1.—Mr. A. B., aged 66, suffered a coronary attack and died suddenly six hours after a cholecystectomy and choledochostomy performed for obstructive jaundice with a septic temperature and cardiac irregularity.

The other 2 patients who died were subjected to early rising and respiratory exercises. Improvement was significant before the terminal stage.

CASE 2.—Mr. J. V., aged 59, died on the fifteenth day after a palliative gastrectomy performed for carcinoma with extension to the pancreas. The patient was out of bed several times daily beginning on the first postoperative day. There was some moisture in the lungs (palpable rales) for the first two days. Coughing exercises in the standing position readily expelled the mucous plugs, with permanent relief by the second day. There was no distention; there was a bowel evacuation on the fifth day and diet was instituted on the sixth. On the eighth day pain developed in the upper right quadrant of the abdomen; this was followed by a subhepatic abscess; the patient was then confined to bed until death.

CASE 3.—Mr. E. D., aged 59, died on the thirty-sixth day after a partial gastrectomy performed in the presence of cholangitis. (The preoperative diagnosis was biliary disease.) Exploration revealed a chronic perforated gastric ulcer walled off by the pancreas (not visualized by roentgen rays). Accidental rupture of the ulcer demanded gastric resection. The patient was out of bed several times daily for respiratory exercises, occasionally taking a few paces. There was some moisture in the lungs (palpable rales) for several days. Coughing exercises in the standing position readily expelled the mucous plugs. He was never able to take food. Atresia of the stoma was anticipated, and distress was controlled by Wangensteen suction. He was not constantly confined to bed until the twenty-third day. Death was due to hepatitis and inanition.

In the following 2 cases the pulmonary complications, which were the gravest in the entire series, were readily controlled. The elimination of moisture from the lungs through coughing exercises in the standing position is noteworthy.

CASE 4.—Mrs. A. S., aged 58, unusually obese, was critically ill for eleven days with empyema of the gallbladder. She had a septic temperature of 104 F., and a pulse rate of 120 before surgical intervention. The upper right quadrant of the abdomen was a solid mass of inflammation. The gallbladder was perforated but walled off by the duodenum and colon and contained thick pus and stones, which were removed. Chemotherapy was applied and drainage instituted. The following day there was intermittent muttering delirium, and rales could be heard outside the room; the patient appeared beyond hope. Coughing in the standing position recovered an enormous amount of thick, purulent mucus. Although the patient could scarcely stand with support, the relief was so gratifying that she requested these exercises repeated as rales recurred; this was several times daily. The lungs remained clear after the third day, and ambulation was instituted. On the seventh day meals were served out of bed; there was a normal bowel evacuation on the eighth day. On the twenty-second day she left the hospital by automobile in excellent condition.

CASE 5.—Mr. L. F., aged 54, was out of bed for respiratory exercises on the first day after a cholecystectomy; the lungs were relatively clear. On the second day a type VII lobar pneumonia developed in the right lung. Specific serum was administered, and chemotherapy was instituted. Coughing exercises in the standing position recovered large amounts of rusty

sputum. These exercises were repeated several times daily. By the fourth day the temperature and pulse remained normal, and ambulation was instituted. By the seventh day the patient felt well and wanted to go home; permission was granted on the ninth day. There were no sequelae.

There was 1 case of dehiscence, associated with pronounced avitaminosis, and not to be charged to early rising.

CASE 6.—Mr. W. M., aged 41, had annular carcinoma of the sigmoid flexure, diagnosed preoperatively by means of a roentgenogram. Exploratory laparotomy through a left rectus incision revealed pronounced distention and engorgement of the descending colon from the splenic flexure to the anus. Extensive rales were present on the following day; the mucus was eliminated by coughing exercises in the standing position. In spite of periodic hallucinations, ambulation was instituted. The distention could not be controlled, a difficulty encountered before operation. On the fifth day it was disclosed that the patient had chronic alcoholism, and that a pyorrhea of weeks' standing had developed into a pronounced generalized stomatitis suggesting a deficiency of the vitamin B complex. Examination revealed dehiscence of the fascial layers. Thereafter he was confined to bed, and the distention and pyorrhea rapidly disappeared when vitamin therapy was employed. An incisional hernia was to be expected.

There was 1 case of thrombophlebitis, the reflex value of which was relieved by injecting procaine hydrochloride into the paravertebral ganglions.

CASE 7.—Mrs. M. B., aged 51, acutely ill with biliary jaundice, chills and fever (102 F.), was subjected to cholecystectomy and choledochostomy for stones and cholangitis. She was out of bed on the first postoperative day. Her chest was clear, and ambulation was gradually instituted. Improvement was rapid, and she left the hospital on the eleventh day. Two days later thrombophlebitis of the left leg suddenly developed. Her temperature was 103 F. and her pulse rate 120. She was rehospitalized. On three consecutive days procaine hydrochloride was injected into the left paravertebral ganglions to block the reflex arc; relief from pain was prompt. The patient was ambulatory after the first day. Her temperature and pulse remained normal after the sixth day, and she was discharged on the twelfth day. Some swelling of the leg was still present two months later.

In a series of 70 herniorrhaphies (46 indirect, 11 direct, 4 femoral, 4 umbilical and 5 incisional), 7 of which were bilateral, there have been 4 recurrences of inguinal hernia and 1 of incisional hernia.

The patients in this series were not from a clinic but private patients with whom I have had almost constant contact. Recently a questionnaire was compiled covering both series, with the following questions: "Did you feel better or worse following early rising?" Over 98 per cent replied favorably; the complaints of the remainder had no bearing whatever on early rising and observation revealed no ill effects in any instance.

SURGICAL TECHNIC AND SUTURES

Spinal anesthesia was routinely employed, and recently the Lemmon technic for fractional spinal anesthesia has been used for the more prolonged operations.

All appendical incisions were of the muscle-splitting type located just external to the linea semilunaris, the rectus sheath being split only when necessary. All incisions for operations on the biliary tract were oblique, bordering on the transverse, just below the costal arch. All incisions for gastric and pelvic operations were midline. There was but 1 midrectus incision (case 6). (Midrectus incisions are not desirable, since sutures in the transversalis fascia are parallel to its fibers.)

All appendical incisions were closed with interrupted single strand 000 chromic catgut.[36] All other incisions were closed with a continuous double strand 000 chromic catgut; the anterior layer of fascia was usually reenforced, particularly

36. As has been previously stated, nylon sutures have been discontinued, since not infrequently granulomas developed months after their use.

in the long incisions, with several interrupted double loop sutures of no. 32 alloy steel wire. In some instances, especially when great tension was present or anticipated, the entire closure was accomplished with double loop interrupted sutures of alloy steel wire according to the Jones technic.[37] Inguinal hernias were all repaired with wire.

POSTOPERATIVE CARE

After the patient's return from the operating room, 2 fluidounces (60 cc.) of water was administered every two hours for the first twenty-four hours. In the presence of abdominal distention or distress, continuous Wangensteen or Miller-Abbott suction was maintained until the condition was relieved. Electrolyte, water and protein balance were controlled by parenteral routes as indicated. Liquid petrolatum was administered daily, usually beginning on the third postoperative day. Cathartics were never given, and enemas were administered rarely, only if digital examination revealed the necessity. Morphine was liberally administered for pain during the first twenty-four hours. Patients were instructed on the day of operation to take deep breathing exercises and were assisted, if necessary, in changing position every hour.

Technic of Getting Patients out of Bed and Associated Exercises.—The morning after operation patients were requested to assume the right lateral position, with the feet over the edge of the bed, and were assisted to a sitting position. They then stood on a stool beside the bed and were urged to cough. By placing the hand at the bases of the lungs during the coughing exercises, the nurse could readily detect rales, if present, and the rales would invariably be eliminated promptly by the expulsion of the mucous plugs. In the presence of moist lungs the respiratory exercises were repeated several times during the day and were continued daily until the lungs remained clear. Usually one such exercise was all that was required. Only occasionally was it necessary to continue coughing exercises to the third day. Ambulation was gradually instituted, the patient taking only a few paces at the first attempt. For patients with the more serious conditions ambulation was not always instituted during the first out of bed period but usually was well established by the second or third day. More recently daily determinations of vital capacity have been made preoperatively and postoperatively, the significance of which is discussed under the heading of vital capacity.

The time of dismissal from the hospital was governed by the well-being of the patient and his desire to go home. Although many patients in this series had hospital insurance, which those in the previous series did not have, the postoperative stay in the hospital for all patients subjected to major operations has been reduced, while the stay for patients subjected to appendectomy remains practically the same.

Follow-Up of Patients.—On dismissal from the hospital patients were instructed to remain active. Patients would appear at the office on the fifth or sixth day after appendectomy for removal of clips; retention sutures would be removed on the seventh or eighth day. Patients on whom other abdominal operations had been performed usually were seen at the office between the ninth and the twelfth day for care of the wound. In most instances these patients were permitted to return to work in one-half the time usually prescribed.

37. This consists of a double loop interrupted suture, the first loop through the fascia and peritoneum, the second through the superficial fascia only; before the ends are ligated they are cut short and bent at right angles (Jones, T. E.; Newell, E. T., Jr., and Brubaker, R. E.: Use of Alloy Steel Wire in Closure of Abdominal Wounds, Surg., Gynec. & Obst. **72**:1056-1059 [June] 1941).

PATHOLOGIC REFLEXES INITIATE CHANGES THAT LEAD TO COMPLICATIONS

The local reaction following an abdominal (or other) incision and the removal of the local lesion does not appear to be the important factor in the development of many of the remote complications that not infrequently threaten the life of the patient. When death does take place, autopsy usually reveals many remote pathologic conditions, such as atelectasis, hypostatic pneumonia, intestinal distention, passive congestion and not infrequently venous thrombosis with infarcts in the vital organs. I shall present evidence from the literature that reflexes from the incision and the traumatized areas have a distinct relationship to the development of many of the complications and that early rising and special respiratory exercises lessen the reactions from these reflexes.

Postoperative Vital Capacity in the Recumbent Position.—The reflex inhibition of the diaphragm, in which the diaphragm assumes a high position and limited excursion after an abdominal operation, and which in turn results in a pronounced diminution in vital capacity and tidal air, is recognized. Patey [38] demonstrated this diaphragmatic inhibition by means of the roentgen rays, while extensive studies have been made of vital capacity (on patients in the recumbent position) before and after surgical procedures, at the Massachusetts General Hospital by Churchill and McNeil [39] and later by Powers,[40] Beecher [41] and Cutler and Hoerr.[42] From their observations it is established that immediately after a surgical procedure on the abdomen there is a pronounced diminution in vital capacity, most evident on the first postoperative day, after which the vital capacity gradually improves, reaching normal usually between the seventh and the fourteenth day (broken lines, charts 1 and 2). The extent and duration of the reduction in vital capacity bear a direct relation to the extent of the surgical procedure. It has been emphasized by Patey [38] and Beecher [41] that the tidal air is diminished in direct ratio to the reduction in vital capacity, which course the tidal air follows in returning to normal. Churchill and McNeil,[39] Beecher,[41] Cutler and Hoerr,[42] Khromov [43] and others emphasized that pulmonary complications increase in direct proportion to the reduction and duration of reduction of vital capacity, while Cutler and Hoerr stated that 50 per cent of all primary postoperative pulmonary complications are established by the end of twenty-four hours and that 90 per cent make their appearance before the end of the fourth day. Incidentally, the presence of pulmonary complications causes a secondary drop in vital capacity, which remains below the normal postoperative level until the complication subsides. The remote systemic changes which may occur as a result of this crippled respiration can be appreciated. Attempts have been made to overcome the reduction of postoperative vital capacity with the hope of decreasing the incidence of pulmonary and other complications. These attempts have not met with any material success.

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38. Patey, D. H.: The Effect of Abdominal Operations on the Mechanism of Respiration, with Special Reference to Pulmonary Embolism and Massive Collapse of the Lungs, Brit. J. Surg. **17**:487-497 (Jan.) 1930.

39. Churchill, E. D., and McNeil, D.: The Reduction in Vital Capacity Following Operation, Surg., Gynec. & Obst. **44**:483-488 (April, pt. 1) 1927.

40. Powers, J. H.: Vital Capacity: Its Significance in Relation to Postoperative Pulmonary Complications, Arch. Surg. **17**:304-323 (Aug.) 1928.

41. Beecher, H. K.: Measured Effect of Laparotomy on Respiration, J. Clin. Investigation **12**:639-650 (July) 1933.

42. Cutler, E. C., and Hoerr, S. O.: Postoperative Pulmonary Complications, Proc. Interst. Postgrad. M. A. North America (1941), 1942, pp. 232-237.

43. Khromov, B. M.: Value of Early Rising After Operation in Prevention of Postoperative Pulmonary Complications, Sovet khir., 1936, no. 9, pp. 389-397.

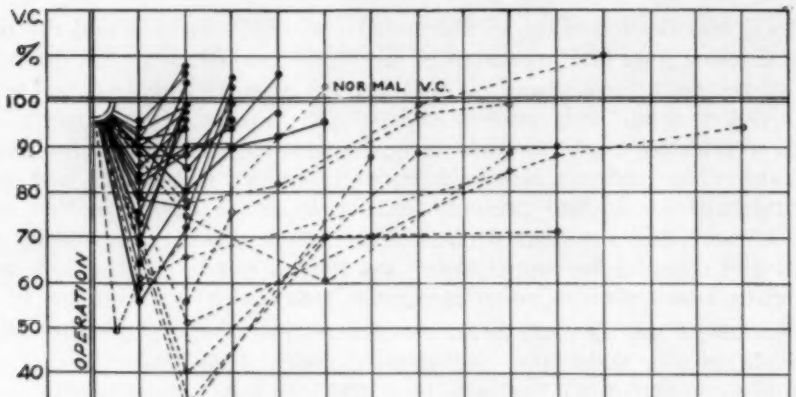

Chart 1.—Heavy lines represent course of vital capacity (daily values) in patients subjected to early rising after appendectomy. Broken lines represent comparable data compiled by Churchill and McNeil [39] for patients not subjected to early rising. (A muscle-splitting incision was used in both series.)

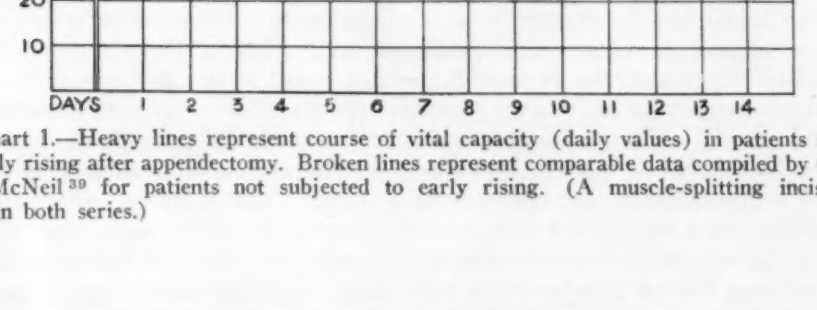

Chart 2.—Heavy lines represent course of vital capacity (daily values) in patients subjected to early rising after operations on the biliary tract (transverse incision). Broken lines represent comparable data compiled by Churchill and McNeil [39] for patients not subjected to early rising (vertical rectus incision).

The Effect of Early Rising on Crippled Respiration.—Readings of vital capacity were made each day for 202 patients subjected to early rising, in the lying, sitting and standing positions before and after surgical procedures on the abdomen. For accuracy, at least three determinations were made in each position. The McKesson-Scott spirometer was employed because of its simplicity of operation. In the final analysis only the vital capacity in the standing position was considered, since there was no material difference in any position. After early rising the vital capacity returned to normal much sooner, usually in less than one-half the prescribed period; convalescence closely followed the improvement in vital capacity. Graphs representing changes in vital capacity following early rising are presented for comparison with Churchill and McNeil's graphs of patients not subjected to early rising. Study of these graphs and the following case reports corroborate these findings (charts 1 and 2).

It was recognized early in these studies that coughing exercises in the standing position would augment rales that could be readily palpated at the base of the lungs—rales which were usually not considered significant or were not detectable when the patient was in the recumbent position. This, I believe, was due to the high, inhibited diaphragm, which in the standing position would be lowered by the downward pull of the abdominal contents, thus opening the collapsed tubules and permitting air to enter. The fact that mucous plugs would then be promptly expelled by coughing (coughing not infrequently automatically induced) supports this contention. Prompt disappearance of rales on expulsion of the mucous plugs by coughing is a specific therapy and a pathognomonic sign of incipient post-operative atelectasis.

Vital Capacity in Early Rising.—The following case reports show a rapid return of vital capacity to normal is a result of early rising. Also note that the course of convalescence was parallel to this curve. This was a characteristic feature in this series.

Case 8.—Mrs. G. P., aged 35, three months pregnant, was suffering with biliary colic. A cholecystectomy was performed for cholelithiasis. She was ambulatory several times on the first postoperative day, and ambulation was increased daily thereafter. Vital capacity before operation was 3.0 liters. Vital capacity on each of the first five postoperative days was as follows: 1.8, 2.6, 2.6, 3.0 and 3.0 liters. The patient asked to leave the hospital on the fifth day; permission was given on the sixth day. She remained active, and no further medical attention was required except removal of retention sutures. She gave birth to twins at term.

Case 9.—Mrs. M. R., aged 37, weighing 287 pounds (130 Kg.), had a cholecystectomy performed for biliary colic. She was ambulatory several times on the first postoperative day, and her lungs were clear. Ambulation was increased daily as tolerated, and by the fourth day she was especially active, even climbing stairs. Vital capacity before operation was 2.6 liters. Daily vital capacity for the first seven days after operation was as follows: 2.0, 2.4, 2.6, 2.6, 2.8, 2.9 and 2.8 liters. The patient asked to leave the hospital on the fifth day, and permission was granted on the seventh day. Retention sutures were removed on the tenth day.

Case 10.—Mr. H. G., aged 30, was subjected to partial gastrectomy for cancer. On the first postoperative day there was incipient atelectasis. Loud rasping rales were present; the temperature was 104 F. and the pulse rate 120. Coughing in the standing position raised large amounts of thick, purulent mucus. The exercises were repeated several times on this day, and by the second day the lungs remained clear. Ambulation began on the third day and increased daily thereafter. On the fifth day the temperature, pulse and function of the bowels were normal. The patient left bed frequently, unaided. On the eighth day he asked to leave the hospital. Permission was granted on the tenth day, and he returned to work on the thirteenth day. There were no sequelae. Vital capacity before operation was 6 liters. On the first ten postoperative days it was 2.0, 3.5, 4.3, 4.0, 4.8, 4.8, 5.8, 5.8, 6.0 and 6.0 liters respectively.

Case 11.—Mr. J. L., aged 47, was operated on for the removal of a diverticulum 5 by 3 by 3 cm. on the outer and posterior surface of the duodenum. The appendix was also

removed. On the first postoperative day extensive palpable rales were present at the bases of both lungs. On coughing in the standing position the mucous plugs were expelled, and ambulation was instituted. By the third day the lungs remained clear. The vital capacity before operation was 5.0. On the first eight postoperative days it was 3.2, 3.8, 4.2, 4.5, 4.7, 5.0, 5.0 and 5.0 liters respectively. He asked to leave the hospital on the sixth day; permission was granted on the eighth day; office care was given on the tenth day.

CASE 12.—Mr. G. G., aged 82, had a gastroenterostomy performed for pyloric obstruction incident to ulcer. He was out of bed on the first postoperative day for respiratory exercises and was ambulatory thereafter. Rales were present the first day, and the patient had auricular fibrillation for three days. There was no urinary retention, and the bowels functioned normally. The vital capacity before operation was 3.4 liters. On the first seven postoperative days it was 3.1, 3.0, 3.0, 2.8, 3.8, 3.8 and 3.8 liters respectively. The patient was dismissed on the seventh day in excellent condition.

CASE 13.—Mr. E. S., aged 16, had acute appendicitis, with a white cell count of 18,500. He was ambulatory the day after appendectomy; his lungs were clear. The preoperative vital capacity was 4.6 liters, and on the first postoperative day the capacity was 4.4 liters. He felt well and left the hospital that afternoon. He had a normal bowel movement the following day and attended the theater in the evening. After the third postoperative day he clerked in a store. Clips were removed on the sixth day.

Note the low preoperative vital capacity due to peritonitis in the following case report.

CASE 14.—Mr. J. B., aged 16, was subjected to appendectomy for rupture of a gangrenous appendix with rapidly spreading peritonitis. His temperature was 102 F. and his pulse rate 144. One hundred and twenty grains (7.75 Gm.) of sulfanilamide was placed in the peritoneal cavity and wound. Suction with a Miller-Abbott tube, parenteral administration of fluids and transfusion of plasma were employed. There were periods of delirium. The patient stood beside the bed several times each day for breathing exercises and was ambulatory on the third day. The vital capacity before operation was 1.0 liter. On the first twelve days after operation it was 2.0, 2.2, 2.1, 2.0, 2.2, 2.2, 2.1, 2.4, 2.4, 2.4, 2.6 and 3.0 liters respectively. Normal bowel evacuation occurred on the third day. The patient left the hospital ambulatory on the twelfth day and was given office care thereafter.

Effect of Reflexes on the Vascular Bed and Functional Activity of Vital Organs.—Postoperative thrombophlebitis of the lower extremities, which so frequently is followed by pulmonary embolism, is considered, at least in part, a reflex phenomenon. By breaking the reflex arc early through the injection of procaine hydrochloride into the paravertebral ganglions, invariably prompt relief is obtained [44] (see case 7). These reflex vascular and functional changes following surgical procedures are not necessarily confined to the lower extremities. It is probable that the vital organs not infrequently are so affected, with or without clinical evidence. For instance, suppression of renal and hepatic function and abdominal distention are common occurrences following the more serious surgical procedures. Pathologic reflexes, to the diaphragm, to the vascular bed and to the vital organs, appear immediately after an incision is made. These reflexes depress respiration, circulation and organic function, thereby promoting anoxia, incomplete metabolism and faulty elimination. Morbidity and complications mount with the intensity and prolongation of these reflexes. Stimulation of respiration and circulation through early rising, deep breathing and coughing exercises, followed by ambulatory activity, is the most effective means of lessening the reactions due to these reflexes and of hastening recovery.

SUMMARY AND CONCLUSIONS

There are several important postoperative reflexes originating from wounds and traumatized areas which initiate pathologic changes leading to complications.

44. Ochsner, A.: Treatment of Thrombophlebitis by Novocain Block of Sympathetics: Technique of Injection, Surgery **5**:491-497 (April) 1939.

The effect of the reflex to the diaphragm can be measured and expressed in the percentage of reduction of vital capacity. In some instances the reduction is over 60 per cent on the first postoperative day, and seven to fourteen days is usually required for vital capacity to return to normal. Pulmonary complications increase in direct proportion to the reduction in vital capacity. Fifty per cent of pulmonary complications are established in twenty-four hours and 90 per cent appear by the fourth day.

In the presence of pulmonary complications coughing in the standing position, if instituted during the first twenty-four hour period (when the vital capacity is at its lowest level), will invariably promptly expel the mucus and cause prompt disappearance of the rales. Repetition of the exercises as occasion demands will invariably maintain clear lung fields.

Coughing in the standing position is particularly effective, since the downward pull of the abdominal contents lowers the diaphragm, permitting air to enter the collapsed tubules beyond the mucous plugs. The lowering of the diaphragm appears to be the explanation why the vital capacity returns to normal so rapidly (in two to seven days) when early rising is instituted.

The curve of postoperative vital capacity is also an index of the stage of convalescence. Recovery after an abdominal operation improves with the improvement of this curve. This is graphically demonstrated in this article by comparable vital capacity curves and case reports. These comparisons emphasize the importance of instituting early rising at the low level of the vital capacity within the first twenty-four hour period. From the literature and my recent observations, I believe the most effective time to be immediately after recovery from the anesthetic.

The effect of early rising on other reflex changes, such as inhibition of the vital organs and reflex vascular changes that lead to thrombosis, has been emphasized.

Dehiscence, incisional hernias and recurrences following inguinal herniorrhaphies were not more frequent after early rising. There was no instance of eventration in the 900 cases. The tensile strength of sutures is greater during the early postoperative period, and healing is promoted through ambulatory activity, as Kimbarovskiy [29] and others have demonstrated. Thus the incision of the patient who rises early should stand the strain more readily than that of the patient who rises at some later date. So far as dehiscence and eventration are concerned, the most dangerous time to get up is between the fifth and the tenth day, the lag period in healing which is not present when early rising is employed.

Limiting confinement to bed to twenty-four hours relieves postoperative distress and rapidly restores the patient to health and to ability to work. This should be of tremendous value during the present emergency, especially to the armed forces, for whom rapid recovery and mobility are so essential.

This practice can be applied to all surgical procedures mentioned in this article in practically all instances, providing the type of incision is well chosen and the wound is properly closed with well selected suture material.

The chief obstacle to early rising is fear and respect for tradition on the part of the surgeon and the patient. Pain and discomfort are insignificant. Even the neurotic or fearful patient, who thinks he is too sick to move, is enthusiastic about early rising once it is established. A common explanation for the presence of complications is, "He got up too soon"; but in reality he got up too late.

Drs. E. D. Churchill and D. McNeil gave permission to copy their graphs on vital capacity. Miss Theresa Aceti carried out the determinations of vital capacity reported in this article. Dr. A. J. Carlson reviewed the entire study and offered criticism and comment.

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CEILING OF UTILIZATION OF NITROGEN

EFFECT OF CONTINUOUS VENOCLYSIS WITH THE AMINO ACIDS OF HYDROLYZED PROTEIN DURING EXPERIMENTAL HYPOALBUMINEMIA

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The correction of protein deficiencies of nutritional origin is a serious quantitative problem whenever the depletion is so severe as to require a large amount of protein alimentation. If but a short time is available for correction, the difficulties are multiplied. Moreover, in many cases the parenteral route must be used. The purpose of the study reported here was to determine if possible the ceiling of utilization of intravenously given amino acids and polypeptides, i. e., how rapidly protein depletions can be corrected. An analogy may be drawn between this problem and that of vitamin deficiencies, many of which may often be corrected completely within a few hours or days by giving sufficiently large amounts of vitamins.

As far as could be determined, no previous observations have been made with intravenous injections of really large doses of mixtures of amino acids. In the St. Louis City Hospital as much as 300 Gm. of hydrolyzed casein daily for three days has been so administered to 2 patients without difficulty.[1] In a study by Brunschwig, Clark and Corbin [2] the greatest amount of the same hydrolysate injected in one day was 150 Gm. for ten consecutive days for a patient weighing 50 Kg.

METHODS

Mongrel dogs were depleted according to the method previously described [3] by putting them on an almost nitrogen-free diet containing a mixture of corn syrup (Karo), Ringer's solution and a vitamin B complex concentrate. Treatment was started after three weeks of this regimen, when hypoalbuminemia was present. A continuous intravenous injection was carried out with the animals suspended in a Pavlov frame. In all cases the total amount of hydrolyzed protein injected was the same as in previous experiments during a week-long period of therapy, i. e., 3.5 Gm. of nitrogen per kilogram of body weight. Urine was collected for the last six or seven days of the depletion period, and during and for six or seven days following venoclysis.

Three experiments were performed, each on 2 dogs as follows:

Experiment 1. The stated amount of hydrolyzed protein as a 10 per cent solution was injected continuously during the course of twenty-four hours. The total volume was 280 cc. per kilogram of body weight. The results are summarized in table 1.

From the Department of Surgery, Washington University and Barnes Hospital.

1. Elman, R.; Weiner, D. O., and Bradley, E.: Ann. Surg. **115**:1165, 1942.
2. Brunschwig, A.; Clark, D. E., and Corbin, N.: Ann. Surg. **115**:1091, 1942.
3. Sachar, L. A.; Horwitz, A., and Elman, R.: J. Exper. Med. **75**:453, 1942.

Experiment 2. In this experiment an equivalent amount of dextrose was added, i. e., a solution containing 5 per cent of the hydrolysate and 5 per cent of dextrose was used. This, of course, doubled the volume of the injected fluid, which was 560 cc. per kilogram of body weight. The results are summarized in table 2.

Experiment 3. In this experiment the continuous venoclysis lasted forty-eight hours instead of twenty-four hours, the daily dose of hydrolysate therefore being one half as large, i. e., 1.75 Gm. of nitrogen per kilogram of body weight. Dextrose was added to the solution, which as made up contained 7.5 per cent of the hydrolysate and 2.5 per cent of dextrose. The total volume injected was 375 cc. per kilogram of body weight. The results are summarized in table 3.

The hydrolyzed protein used was a mixture of amino acids and polypeptides obtained by the enzymic hydrolysis of casein and pork pancreas.[4] During the period of intravenous injections, the usual gavage feedings were omitted.

The chemical methods are the same as those described in previous papers [5]; the plasma volumes were determined by the method as already described.[5a] In estimating the amino acid nitrogen of the urine the method of Sahyun was used.[6]

EXPERIMENTAL OBSERVATIONS

The intravenous injections were tolerated well in all cases; the rate of flow did not in any instance produce vomiting. However, if the rate was not maintained uniformly and the injected fluid flowed much more rapidly even for a period of ten or fifteen minutes, salivation did occur. In only 1 instance was the animal sufficiently restless to require the use of a barbiturate. The intravenous flow produced no particular difficulties except that the needle in most cases had to be changed from time to time from one leg to another because of obstruction to the flow, and a transient edema of the injected limb was often observed.

The data listed in tables 1, 2 and 3 reveal increases in serum protein concentration after the injections in all three experiments. Positive nitrogen balance was also achieved during the period of the injections. However, with the twenty-four hour injections (experiments 1 and 2) there was a pouring out of extra nitrogen in the days after the cessation of the intravenous therapy. Moreover, the increase in the concentration of albumin in these experiments was transient. Indeed by the end of the week after the twenty-four hour injections the concentration of albumin had fallen to a level even lower than when treatment was begun, a circumstance which suggests that little if any of the injected material remained as serum protein. That the actual increase was due to hemoconcentration rather than regeneration was indicated by increases both in globulin and in hematocrit value. A similar outpouring of nitrogen in the period after the injection of large amounts of plasma was also observed in previous experiments in this laboratory.[5b]

An important finding was the large amount of amino acids in the urine of one of the dogs in experiment 1. Of the 12 Gm. of nitrogen excreted in the urine during the period of injection, nearly 3 Gm. was present as amino acids. This excessive amount indicates that during rapid injection amino acids are actually spilled in the urine. That the absence of dextrose in the injected fluid was partly responsible is shown by the fact that no such amounts were found in the urine in

4. The trade name of this product is Amigen, and it was furnished by Mead Johnson and Company of Evansville, Ind.

5. (*a*) Elman, R.; Brown, F. A., Jr., and Wolff, H.: J. Exper. Med. **75**:461, 1942. (*b*) Elman, R., and Davey, H. W.: ibid. **77**:1, 1943. (*c*) Sachar, Horwitz and Elman.[3]

6. Sahyun, M.: J. Lab. & Clin. Med. **24**:548, 1939.

TABLE 1.—*Regeneration of Plasma Albumin and Nitrogen Balance Following a Twenty-Four Hour Venoclysis with a 10 Per cent Solution of a Casein Hydrolysate*

Days	Body Weight, Kg.	Hematocrit Value, %	Plasma Albumin, Gm. per 100 Cc.	Plasma Globulin, Gm. per 100 Cc.	Plasma Volume (Dye Method), Cc.	Total Albumin, Gm.	Nitrogen Intake, Gm.	Nitrogen Output in Urine, Gm.
				Dog 1				
1	6.7	41.4	2.77	3.35	...	....	0.07	
14	...	36.9	1.81	3.19	...	....	0.07	
20	6.6	32.8	1.47	2.90	406	5.97	0.42 (6 days)	6.45 (6 days)
21	...	35.2	2.05	4.01	428	8.77	24.04 (1 day)	12.92* (1 day)
22	...	31.0	1.61	3.26	...	....	0.07	5.50
23	...	....	....	....	...	....	0.07	2.12
24	...	....	....	....	...	....	0.07	1.25
25	...	....	....	....	...	....	0.07	0.65
26	...	....	....	....	...	....	0.07	1.60
27	...	27.4	1.42	3.29	...	....	0.07	0.60
								11.72 (6 days)
				Dog 2				
1	11.8	46.3	4.01	2.95	...	....	0.07	
14	....	34.4	2.58	2.52	...	....	0.07	
20	10.2	34.7	2.69	2.57	558	15.0	0.42 (6 days)	8.85 (6 days)
21	....	36.1	3.18	2.99	549	17.5	36.04	†
22	...	28.6	2.63	2.39	...	....	0.07	4.53
23	...	....	....	....	...	....	0.07	1.96
24	...	....	....	....	...	....	0.07	1.91
25	...	....	....	....	...	....	0.07	0.98
26	...	....	....	....	...	....	0.07	1.24
27	...	31.8	2.44	2.11	...	....	0.07	0.91
								11.53 (6 days)

* Amino acid nitrogen, 2.81 Gm.
† Specimen incomplete.

TABLE 2.—*Regeneration of Plasma Albumin and Nitrogen Balance Following a Twenty-Four Hour Venoclysis with a Solution Containing 5 Per Cent of a Casein Hydrolysate and 5 Per Cent of Dextrose*

Days	Body Weight, Kg.	Hematocrit Value, %	Plasma Albumin, Gm. per 100 Cc.	Plasma Globulin, Gm. per 100 Cc.	Nitrogen Intake, Gm.	Nitrogen Output In Urine, Gm.
			Dog 3			
1	7.8	40.8	3.04	3.01	0.10	
14	7.2	47.2	2.91	3.65	0.10	
20	6.6	36.1	2.49	3.01	0.60 (6 days)	9.82 (6 days)
21 (a. m.)	...	53.6*	3.19	3.67	22.70 (1 day)	9.15 (1 day)
(p. m.)	...	46.2	2.79	3.42	....	amino acid N = 0.84 Gm.
22	...	41.8	2.44	3.10	0	4.12
23	...	....	....	....	0.10	3.13
24	...	....	....	....	0.10	2.39
25	...	....	....	....	0.10	1.99
26	...	....	....	....	0.10	0.72
27	...	33.6	2.29	3.02	0.10	0.61
					0.50 (6 days)	12.96 (6 days)
			Dog 4			
1	11.8	52.3	4.66	2.53	0.16	
14	10.6	52.8	3.61	2.38	0.16	
20	11.0	53.7	3.43	2.58	0.96	15.96 (6 days)
21 (a. m.)	...	61.6*	3.84	2.93	37.84	10.84 (1 day)
(p. m.)	...	55.8	3.51	2.84	.....	amino acid N = 0.85 Gm.
22	...	49.5	3.39	2.75	0	7.79
23	...	....	....	....	0.16	5.46
24	...	....	....	....	0.16	5.74
25	...	....	....	....	0.16	1.56
26	...	....	....	....	0.16	2.01
27	...	37.4	2.89	2.00	0.16	1.60
					0.80 (6 days)	24.04 (6 days)

* Blood taken two hours after the intravenous injection was completed.

experiment 2. On the other hand, it was surprising that better utilization was not induced by the presence of dextrose in this experiment; perhaps the excessive volume of fluid injected was responsible.

In contrast to the findings with the twenty-four hour injection are the permanent results of the forty-eight hour venoclysis. Here there was good nitrogen balance, which, moreover, was followed by no extra excreting of nitrogen in the week following the injection. The increase in serum albumin was also maintained; moreover, its magnitude was similar to that achieved in the week-long period of therapy already reported.[7]

TABLE 3.—*Regeneration of Plasma Albumin and Nitrogen Balance Following a Forty-Eight Hour Venoclysis with a Solution Containing 7.5 per Cent of a Casein Hydrolysate and 2.5 per Cent of Dextrose*

Days	Body Weight, Kg.	Hematocrit Value, %	Plasma Albumin, Gm. per 100 Cc.	Plasma Globulin, Gm. per 100 Cc.	Plasma Volume (Dye Method), Cc.	Total Albumin, Gm.	Nitrogen Intake, Gm.	Nitrogen Output in Urine, Gm.
					Dog 5			
1	13.0	57.5	4.18	3.14	615	25.7	0.07	
7	12.2	53.7	3.64	2.80	...	....	0.07	
14	11.2	54.7	3.51	3.14	...	....	0.07	
22	11.4	50.0	2.95	2.76	...	....	0.07	11.80 (7 days)
26	11.4	51.5	2.74	2.82	571	15.6	45.60	19.15 (2 days)
28	11.4	47.9	3.14	3.23	606	19.0		
35	10.8	45.0	3.18	3.09	...	....	0.07	11.80 (7 days)
					Dog 6			
1	9.0	47.1	4.11	2.22	513	21.1	0.07	
7	8.5	51.4	3.64	2.37	...	....	0.07	
14	7.6	49.9	3.24	2.55	...	....	0.07	
22	8.2	44.6	2.48	2.36	...	....	0.07	7.06 (7 days)
26	7.7	41.5	2.00	2.00	404	10.5	31.20	11.6 (2 days)
28	7.6	38.9	2.98	2.56	451	13.4		
35	7.6	37.2	2.98	2.63	...	....	0.07	8.63 (7 days)

COMMENT

On the basis of the evidence herein presented, it would seem that the body has a much greater capacity for utilizing intravenously administered amino acids and polypeptides than is generally supposed. Thus, in the present experiments, the daily ceiling for the dog was probably above 1.75 Gm. of nitrogen (11 Gm. of protein) per kilogram of body weight. The practical application of this finding concerns the rapidity with which human protein deficiencies can be corrected. Certainly the usual "1 Gm. of protein per kilogram per day" is small in comparison with the probable capacity of the body to assimilate protein once the building stones are absorbed. Indeed, observations have been made by Hartmann and his associates [8] on growing children which show that as much as 10 Gm. of protein per kilogram per day could be assimilated. Such a dose approaches the level achieved in experiment 3 in which a continuous intravenous injection was carried out for forty-eight hours. Whether such a high level of intake could be retained and utilized as well for longer periods remains for further study.

7. Elman, R.; Sachar, L. A.; Horwitz, A., and Wolff, H.: Regenerating Serum Albumin with Hydrolyzed Protein in Chronic Hypoproteinemia Produced by Diet, Arch. Surg. **44**:1064 (June) 1942.

8. Hartmann, D. F.; Meeker, C. S.; Perley, A. M., and McGinnis, H. G.: J. Pediat. **20**:308, 1942.

Of incidental interest are the figures for increase in total albumin observed in experiment 3. It will be noted that in dog 5, 3.4 Gm. of serum albumin was regenerated during the forty-eight hours during which 26.45 Gm. of nitrogen was retained. This amount of nitrogen would correspond ($\times 6.25$) to 165 Gm. of protein. The increase in serum albumin, therefore, represents 2.1 per cent of the nitrogen retained. In dog 6 the proportion is 2.4 per cent. In another paper [3] it was pointed out that of the nitrogen retained in correcting a nutritional deficiency but a small percentage becomes available for synthesis of serum albumin. The figures obtained in these observations were somewhat higher than 2.1 and 2.4 per cent, but the general inferences are similar.

SUMMARY

Positive nitrogen balance as well as regeneration of serum albumin was demonstrated in protein-depleted dogs when 1.75 Gm. of nitrogen per kilogram per day was given for two days by means of a continuous venoclysis, an enzymic hydrolysate of casein containing a mixture of amino acids and polypeptides being used as the sole source of nitrogen. When this same total dose of nitrogen was given during twenty-four hours there was evidence of much less complete utilization.

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